

# ANNALS OF INTERNAL MEDICINE

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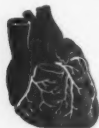
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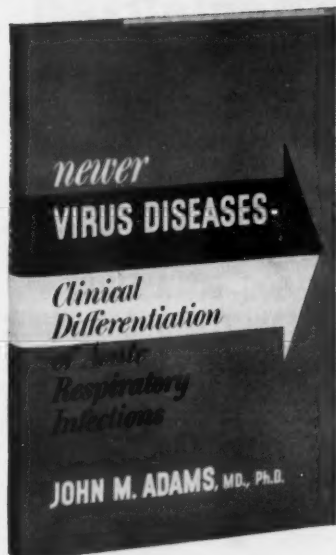


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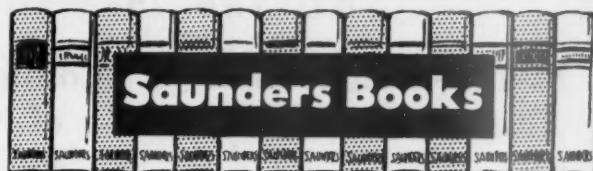
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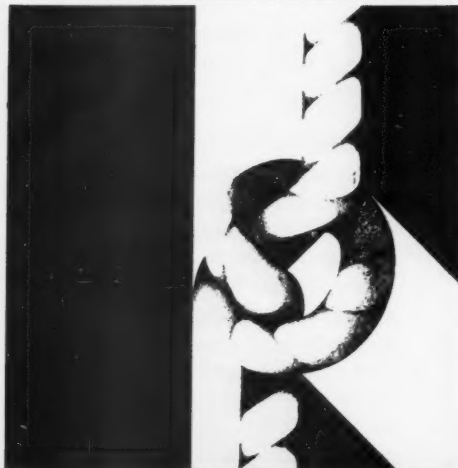
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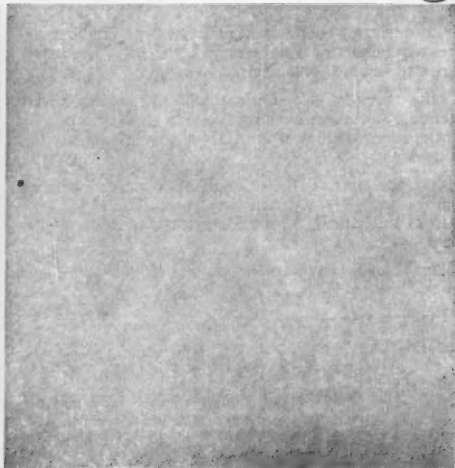
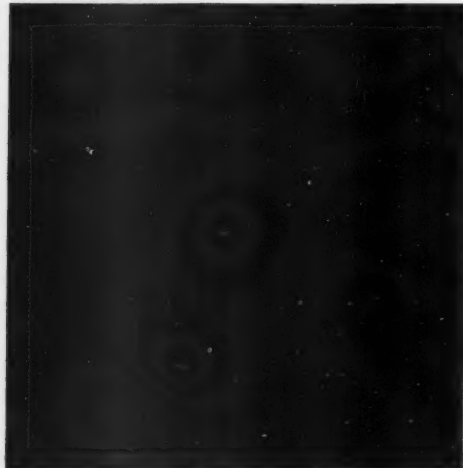


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atherosclerosis "...has been shown to afflict about 77% of American males as early as in the 20-to-30 age range."<sup>5</sup> With MER/29 you have a new, well-tolerated means of lowering cholesterol—considered "...the *sine qua non* of the atheromatous lesion."<sup>6</sup>

**compatible with other cardiovascular therapies:** MER/29 can be used along with other measures to control anxiety, hypertension, obesity, and other conditions associated with cardiovascular disorders. These include anticoagulants, nitroglycerin, and PETN.

**safety data:** Patients have now been treated with MER/29 for relatively long and continuous periods. In no case has there been evidence of serious toxic effects on the function of any vital organ or system. However, since long-term MER/29 therapy may be necessary, periodic examinations, including liver function tests, are desirable. Side effects (nausea, headache, dermatitis) are rare and have usually been associated with dosages greater than those recommended for effective therapy.

**contraindication:** Pregnancy. Since MER/29 inhibits cholesterol biosynthesis, and cholesterol plays an important role in the development of the fetus, the drug should not be administered during pregnancy.

**supplied:** Bottles of 30 pearl gray capsules.

- 
- ... the first cholesterol-lowering agent to inhibit the formation of excess cholesterol within the body, reducing both tissue and serum cholesterol
  - ... no demonstrable interference with other vital biochemical processes reported to date
  - ... convenient dosage: one 250 mg. capsule daily before breakfast
  - ... toleration and absence of toxicity established by 2 years of clinical investigation

# MER/29

(triparanol)

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TRADEMARK: MER/29

## "comprehensive" multivitamins—friend or foe?



Although not itself harmful, the small amounts of folic acid in "comprehensive" multivitamins can correct significant blood disorders to confuse the diagnosis and delay the treatment of pernicious anemia victims.<sup>1-13</sup> Peripheral blood and bone marrow data may appear normal<sup>1</sup> in such patients while accompanying nerve degeneration continues. Diagnosis delayed by normal appearing indices can thus allow irreparable neurologic damage to occur before the true nature of the disease is recognized and treatment begun.<sup>4</sup>

To help physicians avoid this threat, Robins has formulated Adabee®, a new therapeutic multivitamin without folic acid, that is especially safe for long-term nutritional therapy in patients who require maximum support.

### why no vitamin B<sub>12</sub> in Adabee®?

In order to obtain therapeutic levels of specific vitamins for certain individual deficiencies, doctors must often employ a "comprehensive" multivitamin.<sup>4,7</sup> Many such elongated formulas include as ingredients substances which are nonessential, expensive to the patient, and irrational.<sup>4,7,10</sup>

On the basis that B<sub>12</sub> in therapeutic vitamin mixtures has been described as needless by the A. M. A.,<sup>2</sup> and its unnecessary<sup>8,10,14,15</sup> and indiscriminate use<sup>1</sup> has been criticized by astute hematologists,<sup>7</sup> internists,<sup>10</sup> pathologists,<sup>12,13</sup> and nutritional workers,<sup>2</sup> this member of the B-complex has also been omitted from Adabee.

In a rational formula,<sup>2,4,16,17</sup> the need for hormones, enzymes, amino acids, or yeast is not supported. And since these superfluous substances might encumber the desired response to concurrently administered drugs, they are not found in the Adabee formulas.

Each yellow, capsule-shaped Adabee® tablet contains:

Vitamin A .....	25,000 USP units
Vitamin D .....	1,000 USP units
Thiamine mononitrate (B <sub>1</sub> ) .....	15 mg.
Riboflavin (B <sub>2</sub> ) .....	10 mg.
Pyridoxine HCl (B <sub>6</sub> ) .....	5 mg.
Nicotinamide (niacinamide) .....	50 mg.
Calcium pantothenate .....	10 mg.
Ascorbic acid (vitamin C) .....	250 mg.

Each green, capsule-shaped Adabee®-M tablet contains Adabee, plus nine minerals:

Iron .....	15.0 mg.
Iodine .....	0.15 mg.
Copper .....	1.0 mg.
Manganese .....	1.0 mg.
Magnesium .....	6.0 mg.
Zinc .....	1.5 mg.
Potassium .....	5.0 mg.
Calcium .....	103.0 mg.
Phosphorus .....	80.0 mg.

### references:

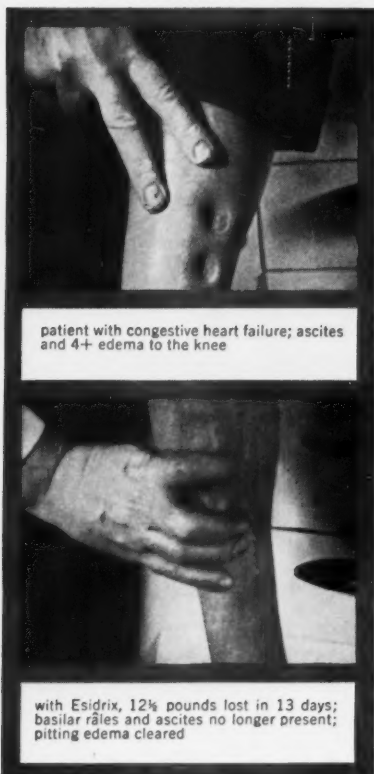
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the multivitamin without folic acid... or B<sub>12</sub>

## new! Adabee®

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patient with congestive heart failure; ascites and 4+ edema to the knee

with Esidrix, 12½ pounds lost in 13 days; basilar râles and ascites no longer present; pitting edema cleared

Photos used with permission of the patient.

# NEW ESIDRIX-K<sup>®</sup>

New ESIDRIX-K provides all the oral diuretic-antihypertensive advantages of ESIDRIX, plus a generous potassium supplement. ESIDRIX produces marked excretion of salt and water in edematous patients, and in many hypertensive patients significantly reduces blood pressure, alone or with other antihypertensive drugs. Potassium excretion is minimal, and the built-in K supplement further helps eliminate problems due to potassium loss. Three ESIDRIX-K tablets provide potassium equivalent to one quart of fresh orange juice; ESIDRIX-K is coated to prevent gastric irritation.

**Complete information sent on request.**

Supplied: Esidrix-K Tablets (white, coated), each containing 25 mg. Esidrix and 500 mg. potassium chloride. Esidrix Tablets, 25 mg. (pink, scored) and 50 mg. (yellow, scored).

Esidrix-K is especially indicated for patients in whom even moderate potassium loss can cause complications, or those whose condition predisposes to hypokalemia. Among candidates for Esidrix-K are patients taking digitalis for congestive heart failure, those with renal or liver disease, those under long-term treatment, and those on salt-restricted diets.

ESIDRIX<sup>®</sup> (hydrochlorothiazide CIBA)

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in edema,  
benefits in  
hypertension  
plus built-in  
potassium  
protection



# Lifts depression...



**You see an improvement within a few days. Thanks to your prompt treatment and the smooth action of Deprol, his depression is relieved and his anxiety and tension calmed—often in a few days. He eats well, sleeps well and soon returns to his normal activities.**

# as it calms anxiety!

For cardiovascular and G.I. patients —

a smooth, balanced action that lifts depression

as it calms anxiety...rapidly and safely

Balances the mood — no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient — they often aggravate anxiety and tension.

And although amphetamine-barbiturate combinations may counteract excessive stimulation — they often deepen depression.

In contrast to such "seesaw" effects, Deprol's smooth, balanced action lifts depression as it calms anxiety — both at the same time.

Acts swiftly — the patient often feels better, sleeps better, within a few days.

Unlike the delayed action of most other antidepressant drugs, which may take two to six weeks to bring results, Deprol relieves the patient quickly — often within a few days. Thus, the expense to the patient of long-term drug therapy can be avoided.

Acts safely — no danger of liver damage.

Deprol does not produce liver damage, hypotension, psychotic reactions or changes in sexual function — frequently reported with other antidepressant drugs.

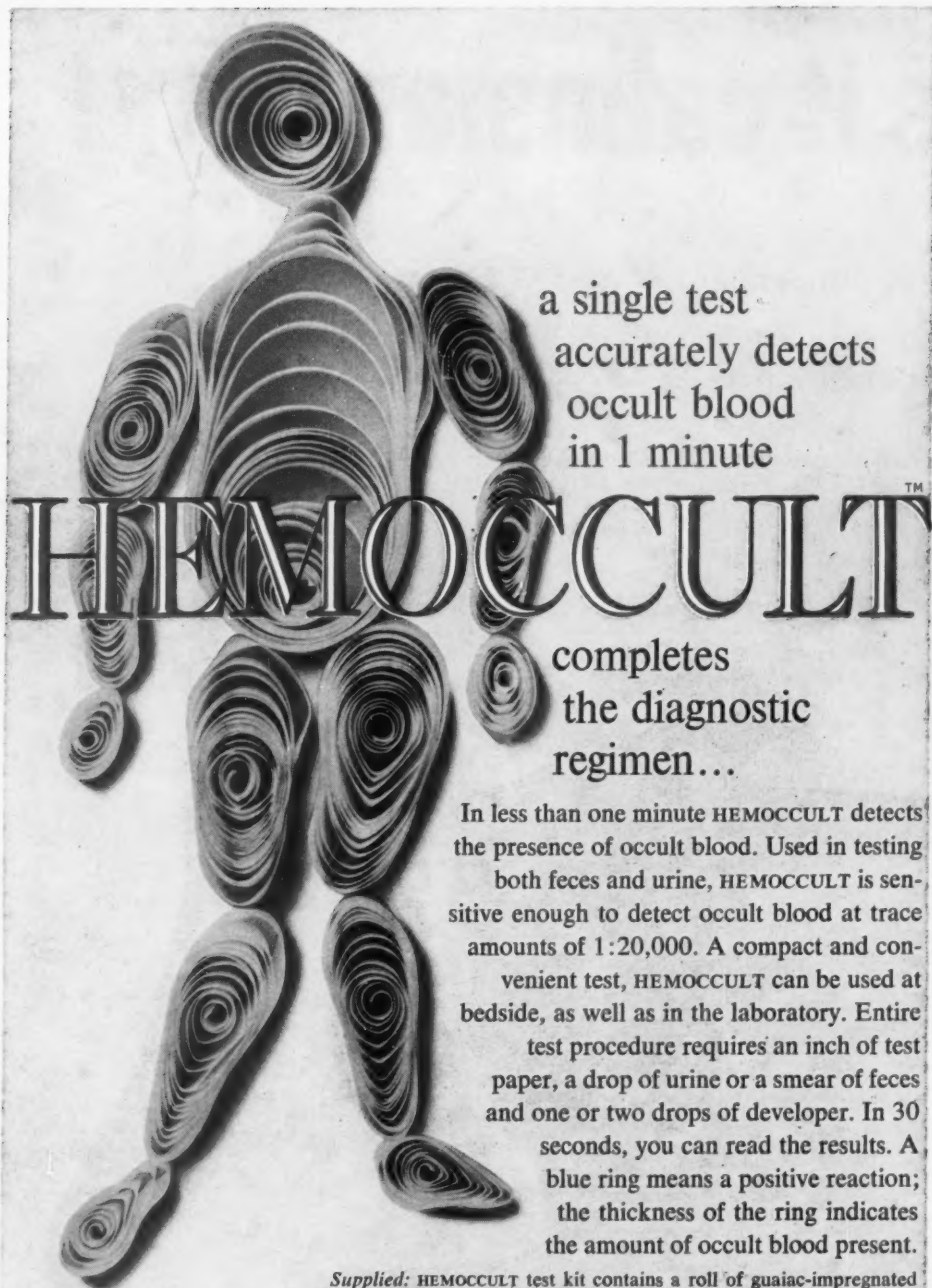
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## Deprol<sup>®</sup>

 WALLACE LABORATORIES/Cranbury, N. J.

**Dosage:** Usual starting dose is 1 tablet q.i.d. When necessary, this dose may be gradually increased up to 3 tablets q.i.d.

**Composition:** 1 mg. 2-diethylaminoethyl benzilate hydrochloride (benactyzine HCl) and 400 mg. meprobamate. **Supplied:** Bottles of 50 light-pink, scored tablets. Write for literature and samples.



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accurately detects  
occult blood  
in 1 minute

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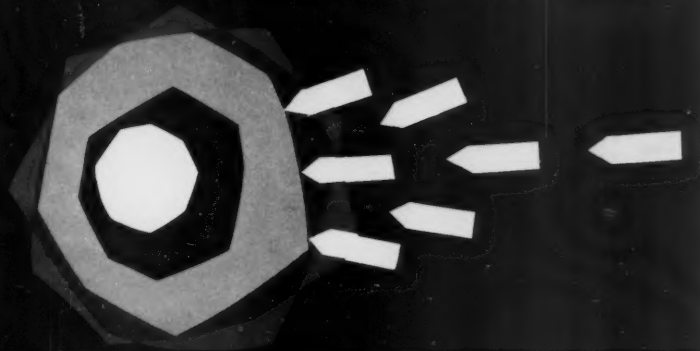


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#### **Inherently sustained action**

Tacaryl possesses inherent long-acting properties. After rapid disappearance from the blood stream, Tacaryl is bound to the tissues. This protective affinity for tissue provides a notably sustained effect which does not depend upon the use of artificial, long-acting construction. The sustained action, an inherent property of the molecule, lasts for periods up to 12 hours.

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Tacaryl is absorbed quickly to provide relief of symptoms within an hour.

#### **low toxicity—minimal side effects**

In studies to date,<sup>1</sup> side effects were minimal; in a small percentage of patients, mild drowsiness was observed. Tolerance was not reported even after long usage. No cumulative effect has been observed.

#### **clinically proved**

In studies of 459 patients,<sup>1</sup> Tacaryl provided effective symptomatic relief in a wide variety of con-

ditions, including allergic rhinitis, pruritus, various skin disorders, allergic bronchial asthma, pruritus of chickenpox, and allergic conjunctivitis. In some cases, the relief of itching bordered on the dramatic.<sup>2</sup> In a double-blind clinical evaluation<sup>3</sup> of various antihistaminic agents in hay fever, Tacaryl provided benefits in all patients with moderate to severe symptoms.

**dosage:** *adults*—One tablet (8 mg.) or two 5 cc. teaspoonfuls syrup (8 mg.) twice daily. *children*—One-half tablet (4 mg.) or one 5 cc. teaspoonful syrup (4 mg.) twice daily.

In some cases it may be desirable to adjust dosage to meet individual requirements.

**supply:** Scored tablets, 8 mg., bottles of 100. Syrup, 4 mg. per 5 cc. teaspoonful, 16 oz. bottles.

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**• USUALLY CLEARS SCALP RINGWORM WITHIN 4 TO 6 WEEKS**

**Dosage:** Adults—250 mg. q.i.d. or 500 mg. b.i.d. Children—According to weight, 250 mg. to 1.0 Gm. daily, in divided doses.

**Supplied:** new 500 mg. scored yellow tablets, bottles of 20 and 100; and 250 mg. scored aquamarine tablets, bottles of 16 and 100. \*

\*Newcomer, V. D., et al.: A.M.A. J. Dis. Child. 99:585, 1960.

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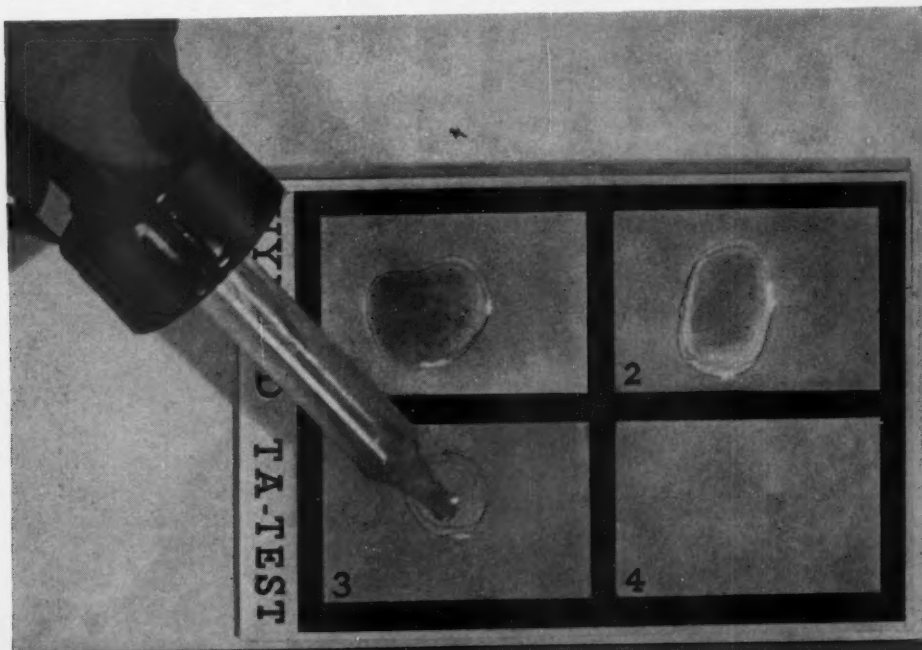
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3. Positive control

*specific  
for  
tension  
headache...*



# *Fiorinal*<sup>®</sup>

*relieves pain,  
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"We have found caffeine, used in combination with acetylsalicylic acid, acetophenetidin, and isobutylallylbarbituric acid, [Fiorinal] to be one of the most effective medicaments for the symptomatic treatment of headache due to tension."

Friedman, A. P., and Merritt, H. H.: J.A.M.A. 163:1111 (Mar. 30) 1957.

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**Each contains:** Sandoptal (Allylbarbituric Acid N.F. X)  
50 mg. (3/4 gr.), caffeine 40 mg. (2/3 gr.), acetylsalicylic acid  
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**Dosage:** 1 or 2 every four hours, according to need, up to 6 per day.



**IS YOUR  
ULCER PATIENT  
SLEEPING  
ON THE JOB?...**



**BECAUSE  
HE CAN'T  
SLEEP  
AT NIGHT?**



In one recent study,<sup>1</sup> new Tral® 75 mg. Gradumet® halted nighttime ulcer pain in 38 of 43 patients who were refractory to the usual measures. Through a "metering" process, Tral 75 mg. Gradumet gives your patient most of the medication when he needs it most—in the middle of the night.

In the above study, 43 patients with refractory duodenal ulcer were given Tral 75 mg. Gradumet—one tablet—every 12 hours. Among the findings: 38 patients—88%—were promptly relieved of nighttime ulcer pain. The other five eventually required surgery. Because nocturnal pain was a symptom in all these patients, its relief, the author felt, was especially noteworthy.

In previous studies,<sup>2,3</sup> the author—employing a 48 hour intubation technique—reported a marked reduction in both volume and acidity of nocturnal gastric secretion in ulcer patients, following administration of Tral 75 mg. Gradumet.

#### **New Form Tailored For Nighttime Use:**

In its new 75 mg. form, Tral Gradumet actually "meters" its release so that the patient is receiving a measured dose of Tral at each point during the sleeping interval. Maximum release is timed to coincide with the critical 2:00 to 4:00 a.m. peak period of nocturnal secretion and discomfort. *The unique Gradumet release principle is not dependent on pH, motility, enzymatic activity or other variables. In fact, the release rate is so predictable that it can be expressed as an algebraic equation.*

## **TRAL 75 mg. GRADUMET**

**AND IN FUNCTIONAL BOWEL DIS-  
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## **TRALCYON™**

**EACH FILMTAB OFFERS 25 mg.  
TRAL PLUS 300 mg. ECTYLUREA**

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a new agent to lyse thrombi

LYOVAC®

# THROMBOLYSIN®

FIBRINOLYSIN (HUMAN)









Results of therapy	Bed rest
<p><b>Effect on intravascular thrombi</b></p>	 <p>Clot may form permanent obstruction to blood flow. New clots may form.</p>
<p><b>Effect on pulmonary emboli</b></p>	 <p>Sudden death from pulmonary embolism is an ever-present hazard. One or more nonfatal pulmonary emboli may result in irreversible lung damage or secondary pneumonia.</p>
<p><b>Effect on duration of illness and convalescence</b></p>	 <p>Weeks of hospitalization or bed rest at home are commonly required in the management of thrombophlebitis, phlebothrombosis, pulmonary embolism, and arterial thrombosis.</p>
<p><b>Frequency and severity of postphlebotic syndrome</b></p>	 <p>Chronic leg swelling, severe secondary varicose veins, and leg ulcers are common sequelae.</p>

In thrombophlebitis, phlebothrombosis, pulmonary embolism, and certain arterial thrombi\*, THROMBOLYSIN makes possible

- lysis of formed clots • reduced mortality and morbidity, shortened hospitalization
  - reduced incidence of postphlebitic complications
- usually fewer severe untoward reactions, such as fever, chills, or malaise; higher degree of safety; greater, more predictable potency.

Supply: Each vial contains 50,000 MSD units.

\*Arterial thrombosis with the exception of cerebral or coronary thrombosis.

Anticoagulant + Bed rest	THROMBOLYSIN + Anticoagulant + Bed rest
 <p>Anticoagulants cannot remove formed clot. However, they may help prevent its extension and may minimize formation of new clots.</p>	 <p>Recently formed intravascular clots are usually lysed rapidly and the formation of new clots may be inhibited. Circulation is usually restored and maintained, with rapid symptomatic relief.</p>
 <p>The careful use of anticoagulants may reduce the occurrence of pulmonary emboli.</p>	 <p>The incidence and severity of pulmonary emboli should be greatly reduced since THROMBOLYSIN may dissolve thrombi before they can become emboli.</p>
 <p>Thromboembolic illness and convalescence may be shortened.</p>	 <p>A striking reduction is usually observed in the duration of hospital stay, bed rest, and convalescence.</p>
 <p>The incidence and severity of the postphlebitic syndrome may be reduced.</p>	 <p>Postphlebitic complications may be prevented or minimized.</p>



For additional information, write to Professional Services, Merck Sharp & Dohme, West Point, Pa.  
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THROMBOLYSIN IS A TRADEMARK OF MERCK & CO., INC.

**RECOVERY RATE: OVER 90%**  
...in over 1,000 published cases  
of thromboembolic disease



*"... at present, this is the oral  
anticoagulant of choice."<sup>1,2</sup>*

- noncumulative
- rapid in action
- uniform in response
- convenient management  
of ambulatory patients

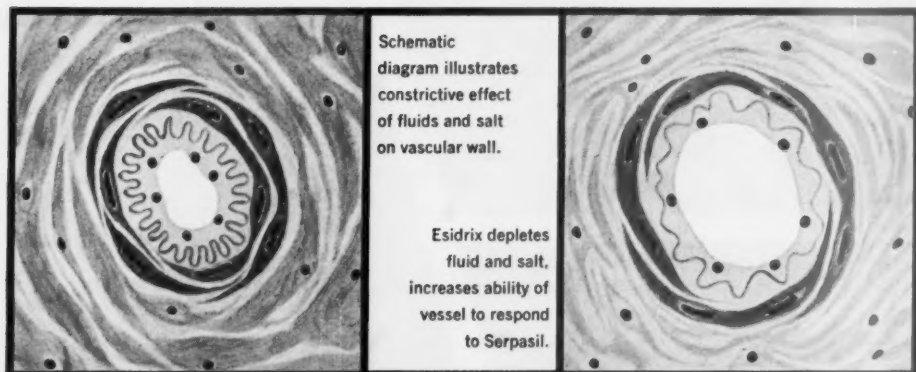
*"... Safe and effective anticoagulant  
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HEDULIN is the trademark for the Walker brand of phenindione. 50 mg. scored tablets for therapeutic use; 20 mg. scored tablets for prophylactic use. Bottles of 100 and 1,000. For more detailed information and a clinical trial supply of Hedulin, write to Walker Laboratories, Inc., Mount Vernon, N. Y. 1. Breneman, G. M., and Priest, E. McC.: *Am. Heart J.* 50:129 (July) 1955. 2. Tandowsky, R. M.: *Am. J. Cardiol.* 3:551 (April) 1959.

## Why combining Esidrix® with Serpasil® improves control of high blood pressure

The presence of excess tissue fluids and salt can keep constricted blood vessels from dilating fully in response to antihypertensive drugs. ■ This may explain why the antihypertensive effect of Serpasil-Esidrix is better than average. By depleting fluid and electrolytes from surrounding tissue, Esidrix enables blood vessels to dilate to physiologic limits. Result: Peripheral resistance is reduced and blood pressure goes down—often to lower levels than can be achieved with single-drug therapy.

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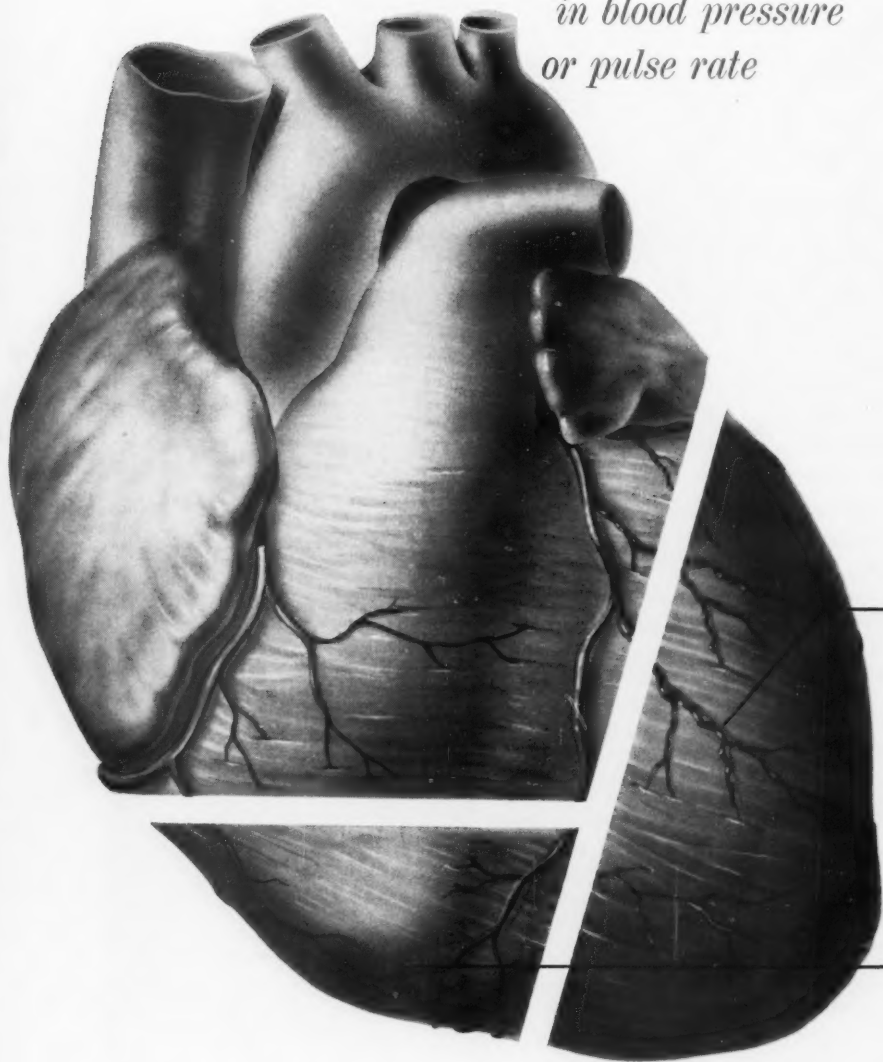
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SERPASIL®-ESIDRIX® (reserpine and hydrochlorothiazide CIBA)

# SERPASIL®-ESIDRIX®

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*improve coronary  
blood flow with  
no significant change  
in blood pressure  
or pulse rate*





*In angina pectoris*, the gradual, prolonged action of Peritrate avoids significant drop in blood pressure, increase in pulse rate, and typical nitrate headache. Peritrate reduces frequency and severity of anginal attacks in 4 out of 5 patients, increases exercise tolerance, reduces nitroglycerin dependence, improves ECG findings.

*In postcoronary management*, gradual, prolonged action helps establish and sustain collateral circulation safely, to reduce the extent of myocardial damage, support natural healing and repair, and minimize any ensuing anginal attacks.

*basic in coronary artery disease*

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brand of pentaerythritol tetranitrate



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NEW form available:  
Peritrate with Phenobarbital Sustained Action.  
1 tablet on arising and 1 tablet 12 hours later.

## restore plasma volume before time runs out

When shock dominates any emergency scene, ALBUMISOL 5% gives you an immediate natural way to restore plasma volume and protein. In administering ALBUMISOL—the protein most responsible for the osmotic pressure of plasma—there is . . .

- no danger of hepatitis
- no waiting for typing, cross-matching, grouping

ALBUMISOL 25% (salt-poor) is also available to help you manage the nutritive deficiencies and severe fluid retention of advanced cirrhosis and nephrosis.

Supplied: ALBUMISOL 5% in 250-cc. and 500-cc. bottles. ALBUMISOL 25% (salt-poor) in 20-cc. and 50-cc. bottles.

# Albumisol®

NORMAL SERUM ALBUMIN (HUMAN)

*ready for immediate blood volume replacement*

ALBUMISOL is a trademark of Merck & Co., Inc.



MERCK SHARP & DOHME, Division of Merck & Co., Inc., West Point, Pa.



**THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN  
URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—  
WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.**



---

**“Thiosulfil” Forte**

---

See over for therapy in difficult patients ►

**HOW TO IMPROVE THE PROGNOSIS IN THE DIFFICULT PATIENT WITH URINARY TRACT INFECTION: Proof of effectiveness and record of safety in long term therapy are two important factors in the selection of a sulfa, particularly when the infection is stubborn and recurrent; occurs during pregnancy; in prostatitis; in patients with indwelling catheters; when stasis is a potential cause of ascending infection. "Thiosulfil" Forte is specially valuable in the treatment of problem patients with urinary tract infection as demonstrated by years of clinical experience.**

### **RECORD OF SAFETY**

In clinical studies of over 3,600 patients, the number of reactions, none serious, was less than 2 per cent.<sup>1-6</sup> "Thiosulfil" was remarkably well tolerated, there being no discontinuation of treatment due to untoward effects, and very few mild reactions were noted."<sup>2</sup> "The drug can be taken over a long period of time with practically no untoward side reactions."<sup>3</sup> "Clinical trial appears to indicate that the drug can be tolerated where other sulfa drugs cannot and that it is effective where some others are not."<sup>4</sup> Out of 3,057 cases . . . 47 patients (1.6%) showed g.i. disturbances and 33 patients (1.1%) allergic reactions.<sup>1</sup> NO REPORTS OF: hemorrhagic dyscrasias, hematuria, anuria, agranulocytosis.

### **PROOF OF EFFECTIVENESS**

A review of more than 3,600 reported cases on "Thiosulfil" demonstrates: a) adequate drug dosage can be simply and economically achieved with a minimum incidence of complicating side effects; b) the antibacterial agent can be given over longer periods of time, particularly in cases involving urinary stasis.

Specific For Urinary Tract Infections: "Thiosulfil" reaches greater urinary concentrations in the active, free, nonmetabolized form than any other sulfa, single or mixed. "Thiosulfil" is rapidly excreted; as much as 79% of the drug is found in the urine after eight hours—of this, 98% is in the active form.<sup>5</sup> The entire g.u. tract is, thus, subjected to continual "sulfa baths" of active drug—more wide spectrum antibacterial activity at site of infection.

Even where urinary stasis exists and cannot be readily corrected, prolonged or even indefinite use of "Thiosulfil" on a reduced dosage schedule will usually keep the infection under control, patients comfortable, and side effects minimal. "Thiosulfil" may materially reduce the likelihood of infections ascending to the parenchyma of the kidneys and subsequent serious systemic involvement.

### **DOSAGE** (Urinary Tract Infections)

TIME PERIOD	DOSE
First two weeks	3 Gm./day <sup>1</sup>
2 weeks to 3 months	2 Gm./day <sup>2, 6</sup>
3 months or longer	0.5 Gm./day <sup>7</sup>

**Suggested Range of Dosage:** 1 or 2 tablets three or four times daily. **Note:** The usual precautions exercised with sulfonamides should be observed.

**Supplied:** No. 786: Each tablet contains 0.5 Gm. sulfamethizole; in bottles of 100 and 1,000 scored tablets.

References — 1. Bourque, J.-P., and Gauthier, G.-E.: Seven years' experience with sulfamethizole, to be published. 2. Bourque, J.-P., and Joyal, J.: *Canad. M.A.J.* 68:337 (Apr.) 1953. 3. Barnes, R. W.: *J. Urol.* 71:655 (May) 1954. 4. Goodhope, C. D.: *J. Urol.* 72:552 (Sept.) 1954. 5. Boger, W. P.: The Antibacterial Sulfonamides: Comparative Studies, Scientific Exhibit Section, American Academy of General Practice Eleventh Annual Scientific Assembly, Apr. 6-9, 1959, San Francisco, California. 6. Cottrell, T. L. C., Rolnick, D., and Lloyd, F. A.: *Rocky Mountain M. J.* 56:66 (Mar.) 1959. 7. Hughes, J., Coppridge, W. M., and Roberts, L. C.: *North Carolina M. J.* 17:320 (July) 1956.

**THE SULFA COMPOUND THAT IS ESPECIALLY VALUABLE IN URINARY TRACT INFECTIONS BECAUSE IT CAN BE GIVEN SAFELY—WITHOUT INTERRUPTION—FOR WEEKS, MONTHS...EVEN YEARS.**

# **"Thiosulfil" Forte**

(BRAND OF SULFAMETHIZOLE)

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*"... Well, I always prescribe Rorer's Maalox. It's an excellent antacid, doesn't constipate and patients will take it indefinitely."*

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MAALOX® an efficient antacid suspension of magnesium-aluminum hydroxide gel offered in bottles of 12 fluidounces.

TABLET MAALOX: 0.4 Gram (equivalent to one teaspoonful), Bottles of 100.

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Samples on request.

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# a new antitussive molecule

alpha-(2-dimethylaminoethyl)-o-chlorobenzhydrol hydrochloride, generically termed "chlophedianol hydrochloride"

## NON-NARCOTIC

# ULO<sup>®</sup>

## SYRUP

### THE ADVANTAGES OF ULO

cough  
suppressant  
action

**equal  
to**

narcotics

duration  
of action

**greater  
than**

narcotics

side  
actions

**less  
than**

narcotics

Though it reaches peak action somewhat more slowly, the cough-suppressant power of ULO is fully as great as that of narcotics.

After reaching peak action, ULO maintains its maximal cough-suppressant effect undiminished for 4 to 8 hours.

ULO is free from the limitations and undesirable side effects of narcotics...no constipation...no nausea...no gastric irritation...no appetite suppression...no tolerance development...no respiratory depression...no drowsiness.

## CLINICAL RESULTS WITH ULO

in 1078 patients observed by 50 U.S. investigators, 46 of whom were chest physicians.

Diagnostic Category	Number of Patients	Results			
		Good to Excellent	Fair	Poor	Not Specified
Upper Respiratory Infection	521	357	88	57	19
Bronchitis	398	309	42	38	9
Pneumonia	53	44	4	5	0
Postnasal Drip	48	32	9	3	4
Tracheobronchitis	32	23	4	3	2
Croup	14	10	2	2	0
Pleurisy	12	11	0	1	0
<b>Total Patients</b>	<b>1078</b>	<b>786</b>	<b>149</b>	<b>109</b>	<b>34</b>
<b>Total Patients Benefited</b>		<b>86.2%</b>			

## Indications

Upper respiratory infections

Common cold

Influenza

Pneumonia

Bronchitis

Tracheitis

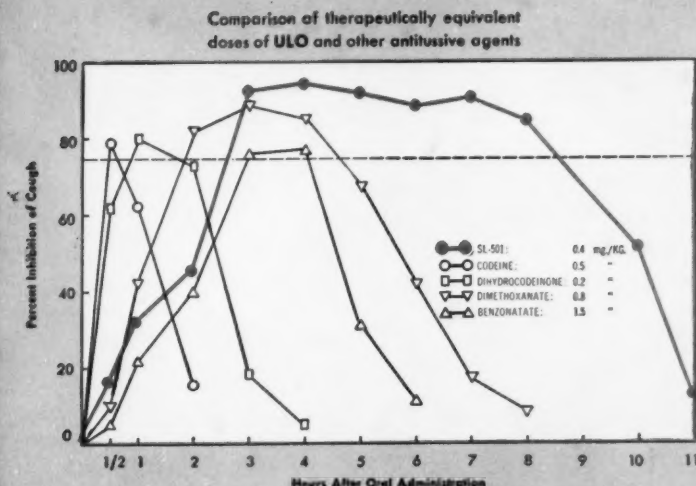
Laryngitis

Croup

Pertussis

Pleurisy

## 4 to 8 hour sustained cough suppression



Mean per cent inhibition of cough in dogs following oral administration of therapeutically equivalent doses of ULO (SL-501) and other antitussive agents. The horizontal dotted line represents threshold of maximum effectiveness, arbitrarily taken at 75 per cent suppression of counted coughs. Note that the duration of maximum effectiveness of a single dose of ULO is 6 hours, 24 times as long as that of codeine. Peak effectiveness of ULO is not reached until 2 or 3 hours after administration, but the maximum antitussive action lasts at least 6 hours.

Chen, J. Y.; Biller, H. F., and Montgomery, E. G., Jr.: *J. Pharmacol. & Exper. Therap.* 128:384, 1960.

### Safety

There are no known contraindications. Side effects occur only occasionally and have been mild. Nausea and dizziness have occurred infrequently, vomiting and drowsiness rarely.

### Dosage:

**Adults:** 25 mg. (1 teaspoonful) 3 or 4 times daily as required;

**Children:** 6 to 12 years of age—12.5 to 25 mg. (1/2 to 1 teaspoonful) 3 or 4 times daily as required;

2 to 6 years of age—12.5 mg. (1/2 teaspoonful) 3 or 4 times daily as required.

### Availability

ULO Syrup, 25 mg. per 5 cc. (teaspoonful) in bottles of 12 fluid ounces.



Northridge, California

New, more effective analgesic

**Kills pain**



# stops tension

For neuralgias, dysmenorrhea, upper respiratory distress, and postsurgical conditions...new compound kills pain, stops tension, reduces fever—gives more complete relief than other analgesics.

Soma Compound is an entirely new, totally different analgesic combination that contains three drugs. First, Soma: a new type of analgesic that has proved to be highly effective in relieving both pain and tension.\* Second, phenacetin: a “standard” analgesic and antipyretic.

Third, caffeine: a safe, mild stimulant for elevation of mood. As a result, the patient gets more complete relief than he does with other analgesics. Soma Compound is nonnarcotic and nonaddicting. It reduces pain perception without impairing the natural defense reflexes.\*

## NEW NONNARCOTIC ANALGESIC

# soma<sup>®</sup> Compound

### Composition:

Soma (carisoprodol), 200 mg.;  
phenacetin, 160 mg.;  
caffeine, 32 mg.

**Dosage:** 1 or 2 tablets q.i.d.

**Supplied:** Bottles of 50  
apricot-colored, scored tablets.

## NEW FOR MORE SEVERE PAIN

# soma<sup>®</sup> Compound + codeine

**BOOSTS THE EFFECTIVENESS OF CODEINE:** Soma Compound boosts the effectiveness of codeine. Therefore, only  $\frac{1}{4}$  grain of codeine phosphate is supplied to relieve the more severe pain that usually requires  $\frac{1}{2}$  grain. **Composition:** Same as Soma Compound plus  $\frac{1}{4}$  grain codeine phosphate. **Dosage:** 1 or 2 tablets q.i.d. **Supplied:** Bottles of 50 white, lozenge-shaped tablets; subject to Federal Narcotics Regulations.

*\*References available on request.*

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## 24 HOURS OF UNINTERRUPTED PROTECTION

WITH ONE TEMPUL®  
MORNING AND NIGHT



### PENTRITOL®

TEMPULES

controlled disintegration  
capsules

**The best has been improved.** PETN, proven over the years to be the most effective drug for preventing anginal attacks, has been improved by incorporating it into controlled disintegration capsules. Pentritol Tempules exhibit the benefits of PETN "...plus a smooth sustained clinical result that seemed to show a superior effect."<sup>1</sup>

Pentritol Tempules given every 12 hours reduced or eliminated nitroglycerin requirements, stopped anginal attacks or reduced their frequency, eliminated or mitigated pain, and increased the capacity for physical activity. *Patients previously taking PETN in tablets with little progress, responded favorably to Pentritol Tempules.*<sup>2</sup>

Recommended dose is 1 Pentritol Tempule morning and evening, approximately 12 hours apart. Available in bottles of 60 Tempules. Also available: Pentritol-B Tempules with 50 mg. of butabarbital added for vasodilation *plus* sedation.

1. Biegeleisen, H. I.: Clin. Med. 2:1005, 1955. 2. Roberts, J. T.: Clin. Med. 4:1375, 1957.

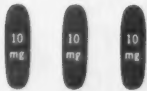

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## In iron-deficiency anemia

The daily  dose of elemental iron in **SIMRON** delivers as much hemoglobin response as this  large amount in other iron salts. That's because **SIMRON** contains Sacagen, a special agent which enhances iron absorption. But, since hemoglobin response is the same, the real advantage in **SIMRON** is this: far less iron ingested means far fewer side effects. **SIMRON** treated patients report no gastric upset, no black stools, no constipation, no diarrhea. Dosage is three capsules daily, between meals. Also Available: **SIMRON PLUS**—when added nutritional factors are indicated.

TRADEMARKS: "SIMRON," "SACAGEN," "SIMRON PLUS" ®

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This effective, practical, readily available medical procedure has been successfully used in treatment of acute renal failure, barbiturate poisoning, intractable edema, hepatic coma, hypercalcemia and chronic uremia, and has been reported useful in acute methyl alcohol poisoning.\*

*Available in 1 liter flasks with administration sets and catheter. Peridial with 1½% dextrose / Peridial with 7% dextrose*

**FOR  
PERITONEAL  
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*\*Stinebaugh, B. J.: A.M.A. Arch.  
Int. Med. 105:613, 1960.*

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In marked contrast to tranquilizers—which often produce an attitude of indifferent calm—'Dexamyl' helps the neurotic, depressed patient to face life with optimism and energy. The patient on 'Dexamyl' often finds it easier to take part in her daily activities.

Dexamyl's positive mood effect is usually apparent within 30 to 60 minutes. This is true whichever form you prescribe (Span-sule® capsules, Tablets, or Elixir). 'Dexamyl' has been used successfully and safely as an antidepressant for more than a decade.

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*"from carcinomatosis to car sickness"*



for faster, more prolonged and  
effective antiemetic action in the  
entire range of emetic situations

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NEW 250 mg CAPSULES

without phenothiazine risks  
without the limitations  
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*Available:* Capsules, blue, 250 mg—bottles of 50.  
*Also available as:* 100 mg Capsules, blue and white.  
Ampuls, 2 cc (100 mg/cc).  
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TIGAN® Hydrochloride—4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride  
Consult literature and dosage information,  
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a lifetime of balanced

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this hypertensive  
patient prefers  
Singoserp . . .  
and so does  
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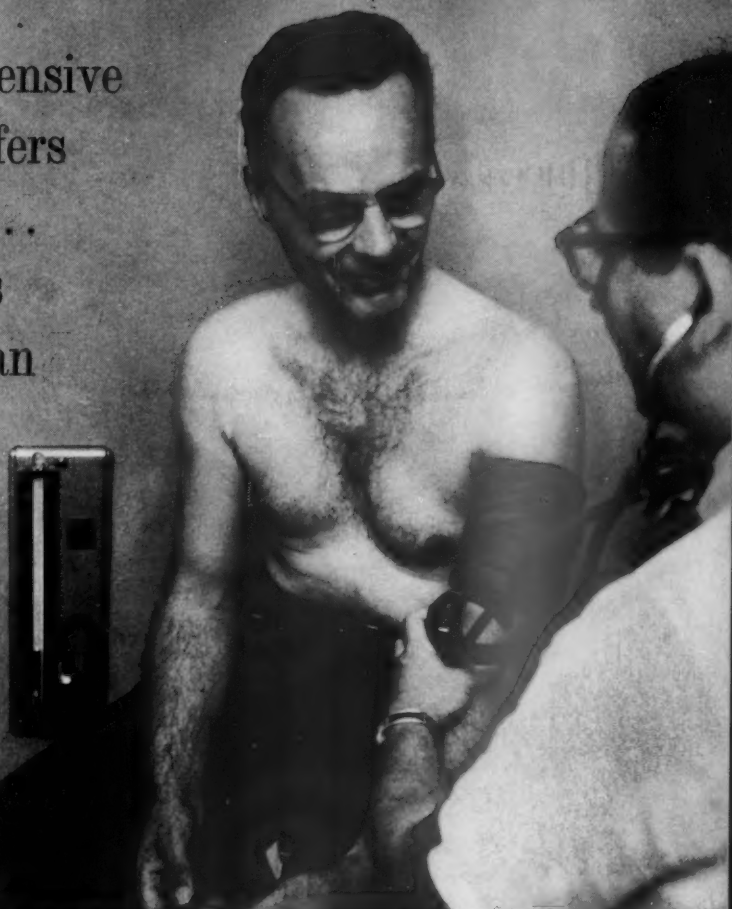


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**Patient's comment:** "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

**Clinician's report:** J. M., a salesman, had a 16-year history of hypertension. Blood pressure at first examination was 190/100 mm. Hg. Whole root rauwolfia lowered pressure to 140/80 — but side effects were intolerable. Singoserp 0.5 mg. daily, further reduced pressure to 130/80 and eliminated all drug symptoms.

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Many hypertensive patients and their physicians  
prefer Singoserp<sup>®</sup> because it usually lowers  
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SUPPLIED: Singoserp Tablets, 1 mg. (white, scored). Also available: Singoserp<sup>®</sup>-Esidrix<sup>®</sup> Tablets #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp<sup>®</sup>-Esidrix<sup>®</sup> Tablets #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. Complete information sent on request.

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# COUMADIN<sup>®</sup>

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COUMADIN is the *original* and *only* warfarin responsible for establishing this drug as closely approaching the ideal anticoagulant.<sup>1,2</sup>

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Over 101,000,000 doses  
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Full range of oral and parenteral dosage forms—COUMADIN\* (warfarin sodium) is available as: Scored tablets—2 mg., lavender; 5 mg., peach; 7½ mg., yellow; 10 mg., white; 25 mg., red. Single Injection Units—one vial, 50 mg., and one 2-cc. ampul Water for Injection; one vial, 75 mg., and one 3-cc. ampul Water for Injection.

Average Dose: Initial, 40-60 mg. For elderly and/or debilitated patients, 20-30 mg. Maintenance, 5-10 mg. daily, as indicated by prothrombin time determinations.

1. Baer, S., et al.: J.A.M.A. 167:704, June 7, 1958. 2. Moyer, K. M.: Diseases of Man, Chicago, Yr. Bk. Feb., Mar., 1960, p. 13.

\*Manufactured under license from the Wisconsin Alumni Research Foundation.

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Milpath acts quickly to suppress hypermotility, hypersecretion, pain and spasm, and to allay anxiety and tension with minimal side effects.

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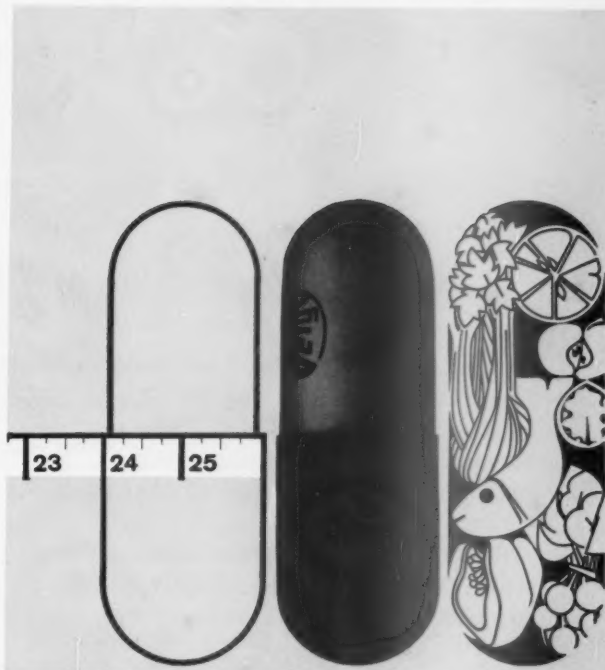
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brand of phenmetrazine HCl with vitamins and minerals

Now, Prelu-Vite helps to fortify the patient's nutritional status and sense of well-being without jeopardizing the success of the weight-reducing program.

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### Availability:

Prelu-Vite<sup>®</sup> - Capsules, each containing 25 mg. of Preludin (brand of phenmetrazine HCl) with vitamins A, B, C and D and 5 minerals.

Under license from C. H. Boehringer Sohn, Ingelheim.

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Preludin<sup>®</sup>Endurets<sup>®</sup>prolonged-action tablets (75 mg.) for once daily administration; and as regular Preludin tablets (25 mg.) for b.i.d. or t.i.d. administration.



321-60



### *on the pathogenesis of pyelonephritis*

"An inflammatory reaction here [renal papillae] may produce sudden rapid impairment of renal function. One duct of Bellini probably drains more than 5000 nephrons. It is easy to see why a small abscess or edema in this area may occlude a portion of the papilla or the collecting ducts and may produce a functional impairment far in excess of that encountered in much larger lesions in the cortex."<sup>1</sup>

Recent experimental evidence in animals strongly supports the view that obstruction of the tubules in the medulla, as opposed to the cortex, predisposes the kidney to pyelonephritis,<sup>2</sup> and "... as few as 10 organisms injected into the medulla were capable of causing infection."<sup>3</sup>

The "exquisite sensitivity"<sup>4</sup> of the medulla to infection highlights the importance of obstruction to the urine flow in the pathogenesis of pyelonephritis. "There is good cause to support the belief that many, perhaps most, cases of human pyelonephritis are the result of infection which reaches the kidney from the lower urinary tract."<sup>5</sup>

An agent, such as FURADANTIN, which has a specific affinity for the urinary tract and which is actively excreted by the cells of the tubules, as well as of the glomeruli,<sup>6</sup> is particularly suited to meet the problems posed by the pathogenesis of pyelonephritis and the primary pathways of infection.



*in pyelonephritis  
to eradicate the pathogens  
no matter the pathway*

# FURADANTIN®

brand of nitrofurantoin

*high urinary concentration  
glomerular filtration  
tubular excretion*

**effective at glomerular and tubular levels:** In addition to simple glomerular filtration, FURADANTIN is actively excreted by the tubule cells.

**rapid antibacterial action:** Antibacterial concentrations of FURADANTIN are in the urine in 30 minutes.

**broad bactericidal spectrum:** FURADANTIN is bactericidal against a wide range of gram-positive and gram-negative bacteria including certain organisms resistant to other agents.

**free from resistance problems:** Development of bacterial resistance to FURADANTIN has not been a problem in over 8 years of extensive clinical use.

**well tolerated—even after prolonged use:** FURADANTIN is nontoxic to kidneys, liver and blood-forming organs. No monilial superinfection, staphylococcal enteritis, proctitis or anovular pruritus has ever been reported.

**no cross resistance or cross sensitization with other drugs:** FURADANTIN, a synthetic nitrofurantoin, is unrelated chemically to any other class of antimicrobial drugs; cross resistance or cross sensitization does not occur.

**AVERAGE FURADANTIN ADULT DOSAGE:** 100 mg. tablet q.i.d. with meals and with food or milk on retiring. **SUPPLIED:** Tablets, 50 and 100 mg.; Oral Suspension, 25 mg. per 5 cc. tsp.

**REFERENCES:** 1. Schreiner, G. E., A.M.A. Arch. Int. M. **102**:32, 1958. 2. Rocha, H., et al.: Yale J. Biol. & Med. **32**:120, 1959. 3. Freedman, L. R.: Yale J. Biol. & Med. **32**:272, 1960. 4. Freedman, L. R., and Beeson, P. B.: Yale J. Biol. & Med. **30**:406, 1958. 5. Rocha, H., et al.: Yale J. Biol. & Med. **30**:341, 1958. 6. Paul, M. F., et al.: Am. J. Physiol. **197**:580, 1959.



**NITROFURANS—a unique class of antimicrobials**

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water-dispersible, antipruritic oil for the bath or shower

Alpha-KERI makes dry skin feel soft and smooth immediately. It effectively deposits a uniform, partially-occlusive oil film over the entire skin area. Alpha-KERI lubricates the skin, relieves itching and restores the protective action of natural skin oils lost by the action of water, weather and detergents. It moisturizes the skin and also helps to retain moisture by retarding evaporation of water. Alpha-KERI contains: Kerolydric<sup>®</sup>, brand of dewaxed, oil-soluble, keratin-moisturizing fraction of lanolin, mineral oil, and a special nonionic emulsifier which provides the right amount of water dispersibility for optimum coverage of the skin with emollient oils. Alpha-KERI oil may be used in the bath, in the shower, for sponge bathing and for infant baths. It can also be used for skin cleansing where soap is contraindicated. Alpha-KERI oil is tinted an attractive green color and pleasantly scented. Bottles of 8 fl. oz. Write for samples and literature.

Westwood Pharmaceuticals, Buffalo 13, New York



“the most effective drug against tremor”<sup>1</sup>

IN PARKINSONISM Parsidol exceeds all other drugs for reducing tremor,<sup>1</sup> a principal impairment of this disease. Parsidol also brightens the patient's outlook and, by lessening rigidity, contributes to restoration of his self-confidence. Especially well tolerated by elderly patients,<sup>1,2,3</sup> Parsidol is effective alone yet is compatible with most other antiparkinsonian drugs.<sup>1</sup> Most patients respond to a maintenance dosage of 50 mg. q.i.d.

**PARSIDOL**® brand of  
ethopropazine  
hydrochloride



relieves tremor  
and rigidity in **PARKINSONISM**

1. Schwab, R. S. and England, A. C.: *J. Chron. Dis.* 8:488 (Oct.) 1958.

2. Schwab, R. S.: *Geriatrics* 14:545 (Sept.) 1959.

3. Doshay, L. J. et al.: *J.A.M.A.* 160:348 (Feb. 4) 1956.

# in edema or

- more doctors are prescribing —
- more patients are receiving the benefits of —
- more clinical evidence exists for —



in congestive failure

"Chlorothiazide was given to 16 patients for a total of 295 patient-treatment days." "Chlorothiazide is a safe, oral diuretic with a clinical effect equal to or greater than a parenteral mercurial." Harvey, S. D. and DeGraff, A. C.: N. Y. State J. Med., 59:1769, (May 1) 1959.



in hypertension

"... our program has been one of polypharmacy in which we attempt to deplete body sodium with chlorothiazide. This drug is continued indefinitely as background medication for all antihypertensive drugs." Moyer, J. H.: Am. J. Cardiology, 3:199, (Feb.) 1959.



in premenstrual edema

"Chlorothiazide is an excellent agent for relief of swelling and breast soreness associated with the premenstrual tension syndrome, since all patients [50] with these complaints were completely relieved." Keyes, J. W. and Berlacher, F. J.: J.A.M.A., 169:109, (Jan. 10) 1959.

DOSAGE: Edema—One or two 500 mg. tablets DIURIL once or twice a day. Hypertension—One 250 mg. tablet DIURIL twice a day to one 500 mg. tablet DIURIL three times a day.

SUPPLIED: 250 mg. and 500 mg. scored tablets DIURIL (chlorothiazide) in bottles of 100 and 1,000.

DIURIL is a trademark of Merck & Co., INC.

Additional information is available to the physician on request.

# Hypertension

# DIURIL<sup>®</sup>

(CHLOROTHIAZIDE)

*than for all other diuretic-antihypertensives combined!*



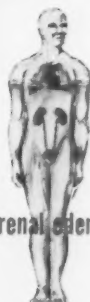
*in edema of pregnancy*

One hundred patients were treated with oral chlorothiazide." "In the presence of clinically detectable edema, the agent was universally effective." "Chlorothiazide is present the most effective oral diuretic pregnancy." Landesman, R., Ollstein, N. and Quinton, E. J.: N. Y. State J. Med., 59:66, (Jan. 1) 1959.



*in cirrhosis with ascites*

"All three of the patients with Laennec's cirrhosis, ascites and edema had a favorable response, with a mean weight loss of 8 lbs., during the five-day treatment period with a slight decrease in edema." Castle, C. N., Conrad, J. K. and Hecht, H. H.: Arch. Int. Med., 103:415, (March) 1959.



*in renal edema*

"In a study of 10 patients with the nephrotic syndrome associated with various types of renal disease, orally administered chlorothiazide was a successful, and sometimes dramatic, diuretic agent." Burch, G. E. and White, M. A., Jr.: Arch. Int. Med., 103:369, (March) 1959.



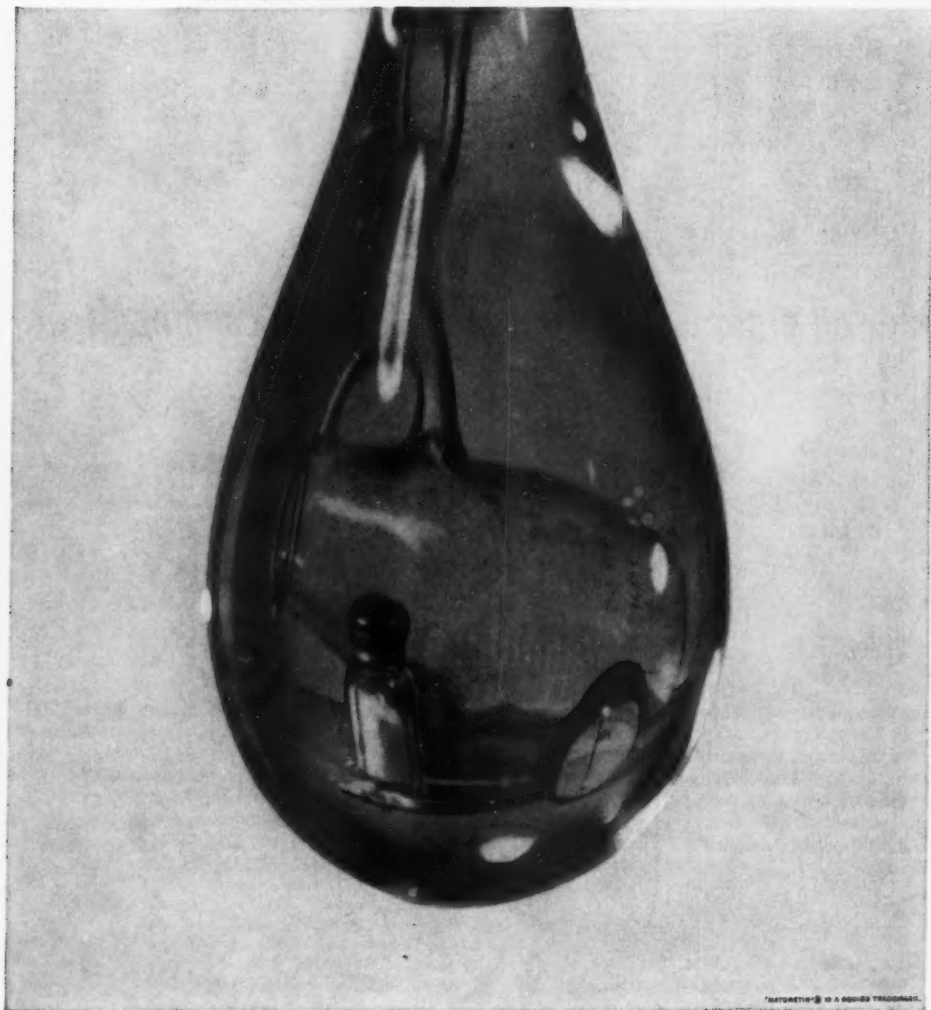
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Division of Merck & Co., Inc., Philadelphia 1, Pa.

## "..extraordinarily effective diuretic.."<sup>1</sup>

Efficacy and expanding clinical use are making Naturetin the diuretic of choice in edema and hypertension. It maintains a favorable urinary sodium-potassium excretion ratio, retains a balanced electrolyte pattern, and causes a relatively small increase in the urinary pH.<sup>2</sup> More potent than other diuretics, Naturetin usually provides 18-hour diuretic action with just a single 5 mg. tablet per day — economical, once-a-day dosage for the patient. Naturetin  $\bar{K}$  — for added protection in those special conditions predisposing to hypokalemia and for patients on long-term therapy.

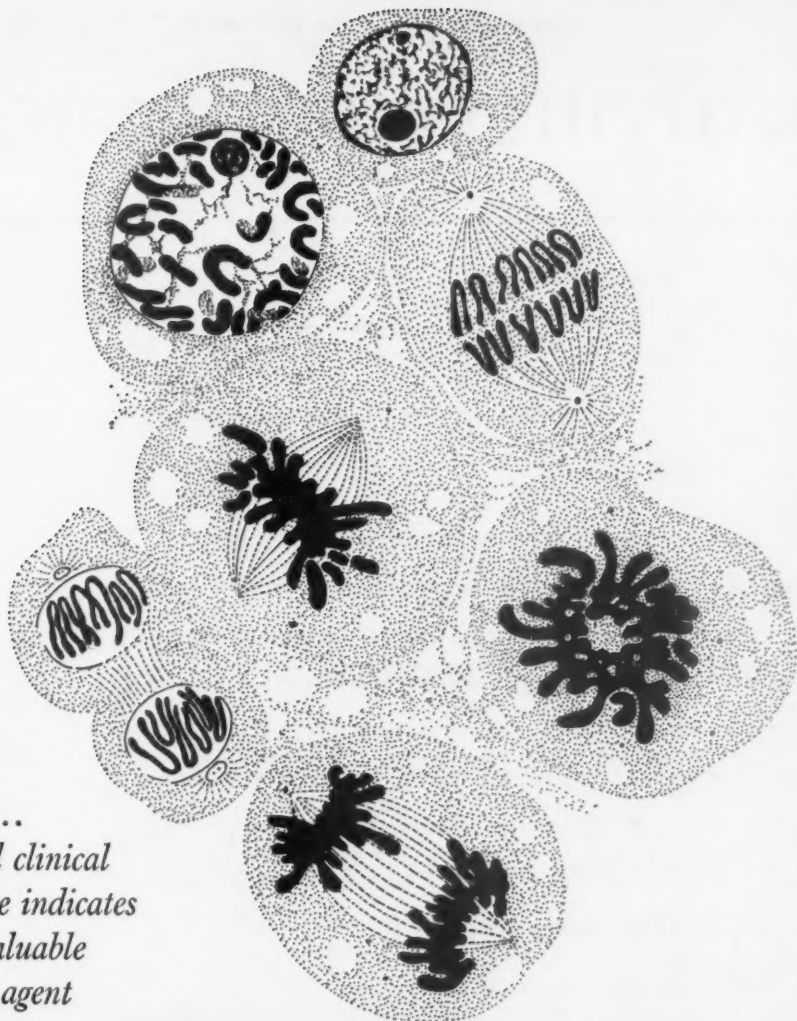
Supplied: Naturetin Tablets, 5 mg., scored, and 2.5 mg. Naturetin  $\bar{K}$  (5  $\bar{K}$  500) Tablets, capsule-shaped, containing 5 mg. benzydrolflumethiazide and 500 mg. potassium chloride. Naturetin  $\bar{K}$  (2.5  $\bar{K}$  500) Tablets, capsule-shaped, containing 2.5 mg. benzydrolflumethiazide and 500 mg. potassium chloride. For complete information consult package circular or write Professional Service Dept., Squibb, 745 Fifth Avenue, New York 22, N. Y. References: 1. David, N. A.; Porter, G. A., and Gray, R. H.: Monographs on Therapy 5:60 (Feb.) 1960. 2. Ford, R. V.: Current Therap. Res. 2:92 (Mar.) 1960.

**Naturetin Naturetin  $\bar{K}$**    
Squibb Benzydrolflumethiazide      Squibb Benzydrolflumethiazide with Potassium Chloride



\*NATURETIN® IS A SQUIBB TRADEMARK.





*new  
evidence...  
continued clinical  
experience indicates  
it as a valuable  
cytotoxic agent*

# CYTOXAN®

*Cyclophosphamide, Mead Johnson*

## FOR PALLIATIVE CHEMOTHERAPY OF CERTAIN TYPES OF MALIGNANT NEOPLASMS

Report from a recent comparative clinical evaluation of two alkylating agents: "With the use of cyclophosphamide [Cytosan], there is a relative lack of thrombocytopenia and a diminution in gastrointestinal side-effects, so that it may offer therapeutic advantages over other alkylating agents."<sup>9</sup>

**Other Advantages in Clinical Practice:** Broad spectrum of application • High therapeutic index • No vesicant activity—may be given orally or parenterally.

For a copy of the Cytosan brochure, or other additional information on Cytosan, communicate directly with the Medical Department (Section B), Mead Johnson & Company, Evansville 21, Indiana.

<sup>9</sup>Papac, R.; Petrakis, N. L.; Amini, F. and Wood, D. A.: J.A.M.A. 172:1387-1391 (March 26) 1960.

11399



**Mead Johnson**  
*Symbol of service in medicine*

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# "Gratifying" relief from

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*for your patients with  
'low back syndrome' and  
other musculoskeletal disorders*

**POTENT** muscle relaxation

**EFFECTIVE** pain relief

**SAFE** for prolonged use

# stiffness and pain

**“gratifying”** *relief from stiffness and pain  
in 106-patient controlled study*

*(as reported in J.A.M.A., April 30, 1960)*

“Particularly gratifying was the drug’s [SOMA’s] ability to relax muscular spasm, relieve pain, and restore normal movement . . . Its prompt action, ability to provide objective and subjective assistance, and freedom from undesirable effects recommend it for use as a muscle relaxant and analgesic drug of great benefit in the conservative management of the ‘low back syndrome.’”

*Kestler, O.: Conservative Management of “Low Back Syndrome”,  
J.A.M.A. 172: 2039 (April 30) 1960.*

**FASTER IMPROVEMENT**—79% complete or marked improvement in 7 days (Kestler).

**EASY TO USE**—Usual adult dose is one 350 mg. tablet three times daily and at bedtime.

**SUPPLIED:** 350 mg., white tablets, bottles of 50.  
For pediatric use, 250 mg., orange capsules, bottles of 50.

Literature and samples on request.

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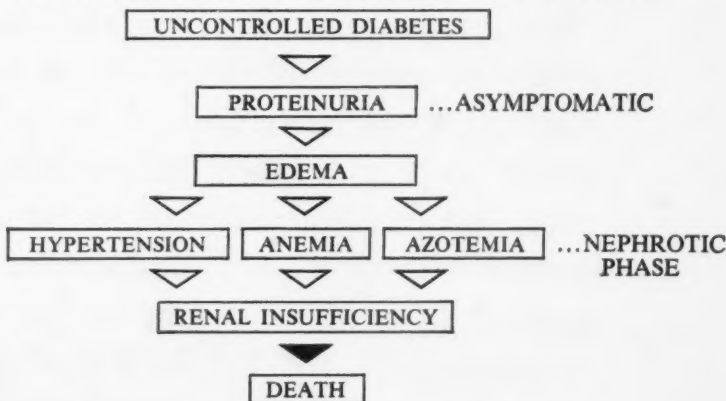
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### *Why is the diabetic especially vulnerable to nephropathy?*

Because the kidney is the body organ most susceptible to alteration in structure and function by the diabetic state. Seventy-five per cent of all deaths due to diabetes result from cardiovascular-renal complications. Of this group, one-fifth of the complications are primarily renal in origin.

Source: Whitehouse, F. W.: Postgrad. Med. 24:54, 1958.

### NATURAL HISTORY OF DIABETIC NEPHROPATHY



Adapted from Whitehouse, F. W.: *op. cit.*

CHECK THE DIABETIC FOR GLYCOSURIA...AND PROTEINURIA  
PROBABLY THE BEST SINGLE INDICATOR OF RENAL DISORDER

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colorimetric "dip-and-read" combination test for *protein* and *glucose* in urine

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In depression

To restore emotional stability  
during the declining years



# Tofrānil

brand of imipramine hydrochloride

Thymoleptic

## New for geriatric use

Tablets of 10 mg.

Recent studies<sup>1-3</sup> strongly indicate underlying depression as a causative factor, and Tofrānil as an eminently successful agent, in restoring the difficult geriatric patient to a more contented frame of mind and more manageable disposition.

1. Cameron, E.: The Use of Tofrānil in the Aged, *Canad. Psychiat. A. J. Special Supplement*, **4**:S160, 1959.
2. Christe, P.: Indications for Tofrānil in Geriatrics, *Schweiz. med. Wchnschr.* **90**:586, 1960.
3. Schmied, J., and Ziegler, A.: Tofrānil in Geriatrics, *Praxis* **49**:472, 1960.

**Also Available:**

For the treatment of non-geriatric depression: Tofrānil tablets of 25 mg. and ampuls of 25 mg. in 2 cc. solution.

 **Geigy**, Ardsley, New York

TO-451-60

benzthiazide

# NaClex<sup>®</sup>

a new molecule  
with an  
unsurpassed  
faculty for  
salt excretion

*A. H. Robins announces NaClex, a potent, oral, non-mercurial diuretic. NaClex is a new molecule, designated benzthiazide. Its unique chemical structure produces a "pronounced increase in diuretic potency"<sup>1</sup> over many older diuretics. NaClex also has antihypertensive properties, and it enhances the activity of other antihypertensive drugs.*





# in diuresis

salt removal  
is still the  
fundamental  
objective

## *As salt goes, so goes edema*

A fundamental principle of diuresis is that "increased urine volume and loss of body weight are proportional to and the osmotic consequences of loss of ions."<sup>2</sup> New NaClex helps reduce edema through the application of this basic principle.

Apparently functioning in the proximal renal tubules, NaClex strictly limits the reabsorption of sodium and chloride ions. To maintain the essential, subtle balance between salt and water, the body's homeostatic mechanism reponds to this loss of ions by allowing an increased excretion of excessive extracellular water. Thus the NaClex-induced removal of salt leads directly to the reduction of edema.

### *How potent is benzthiazide?*

Compared tablet for tablet with oral diuretics now available, NaClex is unsurpassed in potency. Milligram for milligram, it has achieved optimum diuresis in pharmacologic studies at 1/20 the dose required for chlorothiazide.

### *What are the major diuretic indications for NaClex?*

NaClex produces diuresis, weight loss, and symptomatic improvement in edema associated with conditions such as congestive heart failure, cirrhosis of the liver, chronic renal diseases (including nephrosis), premenstrual tension, toxemia of pregnancy, and obesity. Edema of local origin and that caused by steroids may also benefit.

### *To what extent is NaClex useful in hypertension?*

NaClex has definite antihypertensive properties, and may be used alone in mild hypertension. In severer cases it may be used with other antihypertensive

drugs, potentiating them and permitting their use at lower dosage. In hypertension with associated water retention, NaClex is of twofold value. It may be prescribed for congestive heart failure as an ancillary measure to digitalis.

### *Is potassium excretion a problem with NaClex?*

In short-term therapy, excessive potassium excretion is unlikely. In the effective dose range, potassium loss varies from 1/6 to 1/2 that of sodium. Naturally, the ratio of these ions depends on the rate at which excess sodium stores are depleted, and whether salt intake is restricted.

### *Can NaClex and mercurials be given concurrently?*

Yes. When so employed, NaClex may increase the efficacy of mercurials. But NaClex alone is often effective enough to eliminate the need for parenteral mercurial administration. Also, NaClex may be effective in cases when mercurials are not.

**Supply:** Available in yellow, scored 50 mg. tablets.

**References:** 1. Ford, R. V., *Cur. Therap. Res.*, 2:51, 1960. 2. Pitts, R. F., *Am. J. Med.*, 24:745, 1958.

*For complete dosage schedules, precautions, or other information about new NaClex, please consult basic literature, package insert, or your local Robins representative, or write to A. H. Robins Co., Inc., Richmond, Va.*

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In active people who won't take time to eat properly, MYADEC can help prevent deficiencies by providing comprehensive vitamin-mineral support. Just one capsule a day supplies therapeutic doses of 9 important vitamins plus significant quantities of 11 essential minerals and trace elements. MYADEC is also valuable in vitamin depletion and stress states, in convalescence, in chronic disorders, in patients on salt-restricted diets, or wherever therapeutic vitamin-mineral supplementation is indicated.

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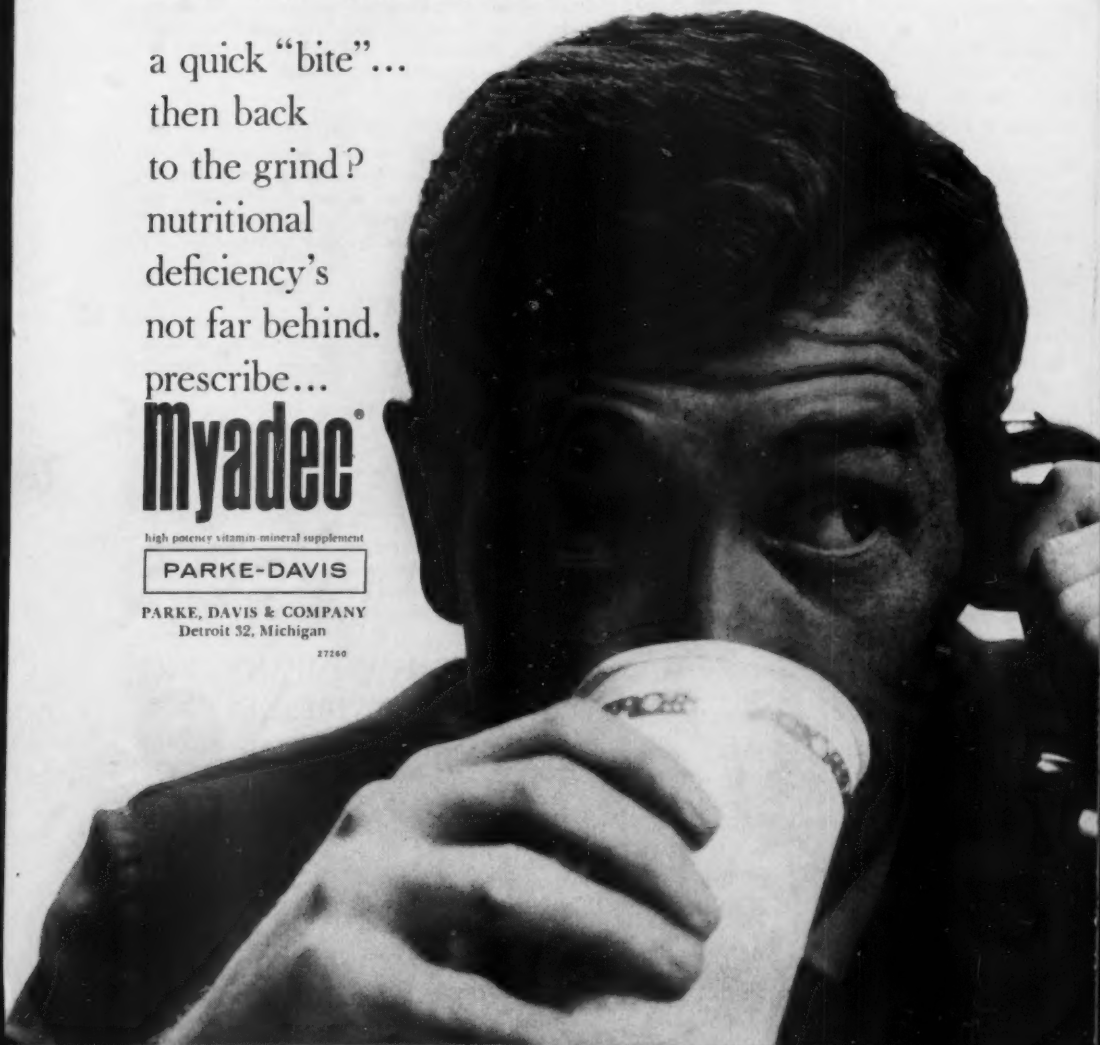
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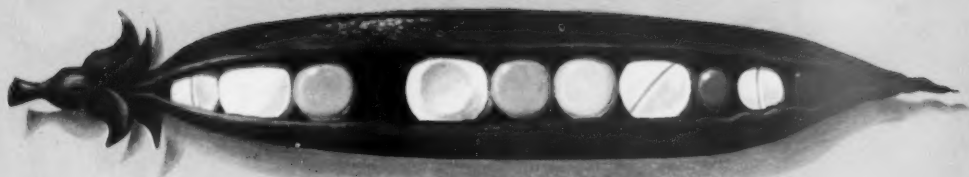
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*how does Mellaril differ from other potent tranquilizers?*



**Mellaril<sup>®</sup>**

THIORIDAZINE HCl



*provides highly effective tranquilization,  
relieves anxiety, tension, nervousness,*

*but is virtually free of such toxic effects as*

jaundice

Parkinsonism

blood dyscrasia

dermatitis



*greater specificity of tranquilizing action results in fewer side effects*



Virtual freedom of Mellaril from major toxic effects is due to greater specificity of tranquilizing action—divorced from such “diffuse” effects as anti-emetic action.

# Mellaril

THIORIDAZINE HCl

*specific, effective tranquilizer*

“A new phenothiazine derivative, thioridazine [Mellaril®], was used to treat 71 patients, most of whom were unduly agitated and disturbed due to hospitalization for medical or surgical conditions....The response to treatment was considered satisfactory in 83.4 per cent of patients....In agreement with the published results of other investigators, we believe that thioridazine shows a greater specificity of tranquilizing action and freedom from serious toxic effects when compared with some of the other phenothiazines.”\*

Supply: MELLARIL Tablets, 10 mg., 25 mg., 50 mg., 100 mg.



\*David, N. A.; Logan, N. D., and Porter, G. A.: Evaluation of Thioridazine (Mellaril), a New Phenothiazine, in The Hospitalized Patient. A.M. & C.T. 7:364 (June) 1960.

**a pair of cardiac patients:**



**both are free of pain—but only one is on**

**DILAUDID®**

(Dihydromorphinone HCl)

**swift, sure analgesia normally unmarred by nausea and vomiting**

DILAUDID provides unexcelled analgesia in acute cardiovascular conditions. Onset of relief from pain is almost immediate. The high therapeutic ratio of DILAUDID is commonly reflected by lack of nausea and vomiting—and marked freedom from other side-effects such as dizziness and somnolence.

● **by mouth**    ● **by needle**    ● **by rectum**

2 mg., 3 mg., and 4 mg.

May be habit forming—usual precautions should be observed as with other opiate analgesics.



**KNOLL PHARMACEUTICAL COMPANY • ORANGE, NEW JERSEY**

## Helps you take the misery out of menopause *as hormones alone often don't do*



### Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

**Dosage:** One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

**Composition:** Miltown (meprobamate) + conjugated estrogens (equine).

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Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

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(Miltown® plus natural estrogens)

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Each tablet contains:

Provera (medroxyprogesterone acetate) 2.5 mg.  
 Cardrase (ethoxzolamide) ..... 35 mg.  
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DOSAGE: 1 tablet 1 or 2 times daily, 5-10 days  
 before the period.

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### to restore hormonal balance...

*corrective therapy* Because Cýtran contains the new progestin, Provera,<sup>†</sup> you can now reach the *cause* of premenstrual tension—hormonal imbalance. Estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Thus even abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are effectively relieved.

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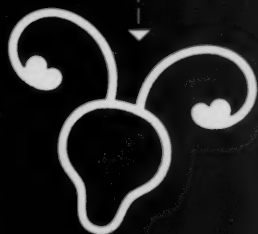


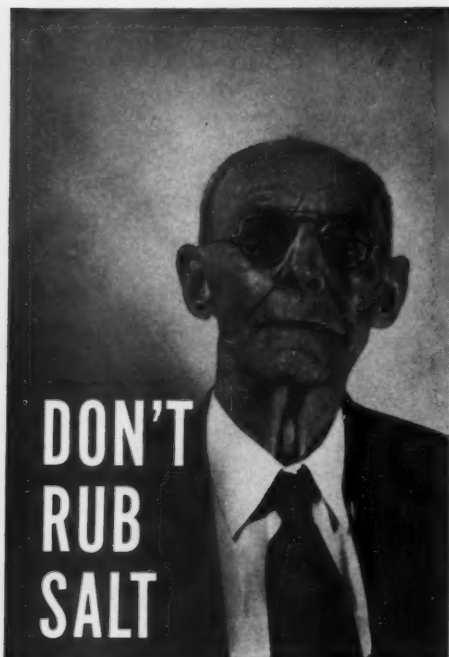
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Modern saluretics may *seem* to have made unlimited salt intake possible for cardiac and hypertensive patients. Yet despite the improvements in diuretic therapy, sodium restriction is still important in the prophylaxis of edema. The wise physician does not add needlessly to the burden of his patient, nor test unnecessarily the power of the drugs he prescribes. It makes good sense to him to prescribe DIASAL—which looks, tastes and flavors food exactly like salt . . . but is sodium free.

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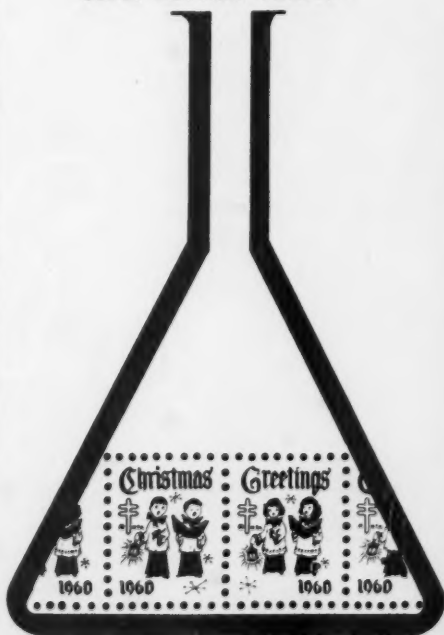
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# HELP SCIENCE FIGHT TB

*One out of every five Americans is infected with TB. Chances are that one out of twenty of those infected will break down with active disease during his lifetime. † Your Christmas Seal contribution can help research find a way to prevent those breakdowns*

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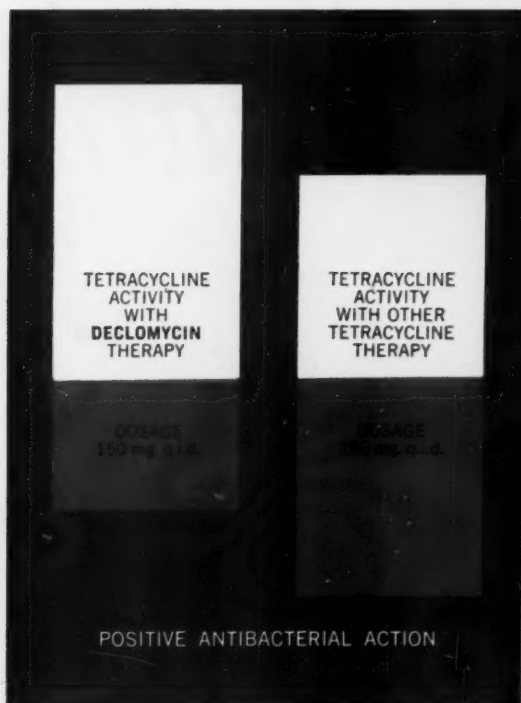


*attains  
sustains  
retains*

*extra  
antibiotic  
activity*

## *extra-activity...promptly attained*

**DECLOMYCIN** Demethylchlortetracycline attains—usually within two hours—blood levels more than adequate to suppress susceptible pathogens. These levels are attained in tissues and body fluids on daily dosages substantially lower than those required to elicit antibiotic activity of comparable intensity with other tetracyclines. With other tetracyclines, the average, effective, adult daily dose is 1 Gm. With **DECLOMYCIN** Demethylchlortetracycline, it is only 600 mg.



# DECLOMYCIN



## evenly sustained long retained

DECLOMYCIN Demethylchlortetracycline sustains, through the entire therapeutic course, the high activity levels needed to control the primary infective process and to check the onset of a complicating secondary infection at the original—or at another—site. This combined therapeutic action is sustained, in most instances, without the pronounced hour-to-hour, dose-to-dose, peak-and-valley fluctuations in activity levels which characterize other tetracyclines.

DECLOMYCIN Demethylchlortetracycline retains significant activity levels, up to 48 hours after the last dose is given. At least a full, extra day of positive antibacterial action may thus be confidently expected. One capsule four times a day, for the average adult in the average infection, is the same as with other tetracyclines—but the **total** dosage is lower and the duration of anti-infective action is longer.

DECLOMYCIN—SUSTAINED ACTIVITY LEVELS

OTHER TETRACYCLINES—PEAKS AND VALLEYS

PROTECTION AGAINST PROBLEM PATHOGENS

DAYS 1 2 3 4 5 6

DAYS OF TETRACYCLINE A<sup>1</sup> DOSAGE

DURATION OF PROTECTION

DAYS OF TETRACYCLINE B<sup>2</sup> DOSAGE

DURATION OF PROTECTION

DAYS OF TETRACYCLINE C<sup>3</sup> DOSAGE

DURATION OF PROTECTION

DAYS OF DECLOMYCIN DOSAGE

DURATION OF PROTECTION

(1) Oxytetracycline. (2) Chlortetracycline. (3) Tetracycline.

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- higher activity/intake ratio—positive antibacterial action
- sustained activity levels—protection against problem pathogens
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**Dosage:** 1 to 2 drops (3 to 6 mg.) per pound body weight per day—divided into 4 doses.

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added measure  
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**PRECAUTIONS:** As with other antibiotics, DECLOMYCIN may occasionally give rise to glossitis, stomatitis, proctitis, nausea, diarrhea, vaginitis or dermatitis. A photodynamic reaction to sunlight has been observed in a few patients on DECLOMYCIN. Although reversible by discontinuing therapy, patients should avoid exposure to intense sunlight. If adverse reaction or idiosyncrasy occurs, discontinue medication.

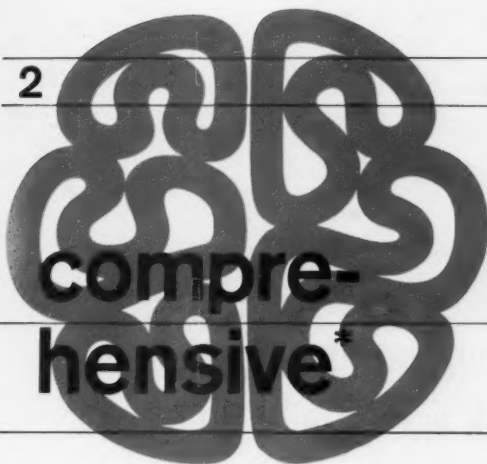
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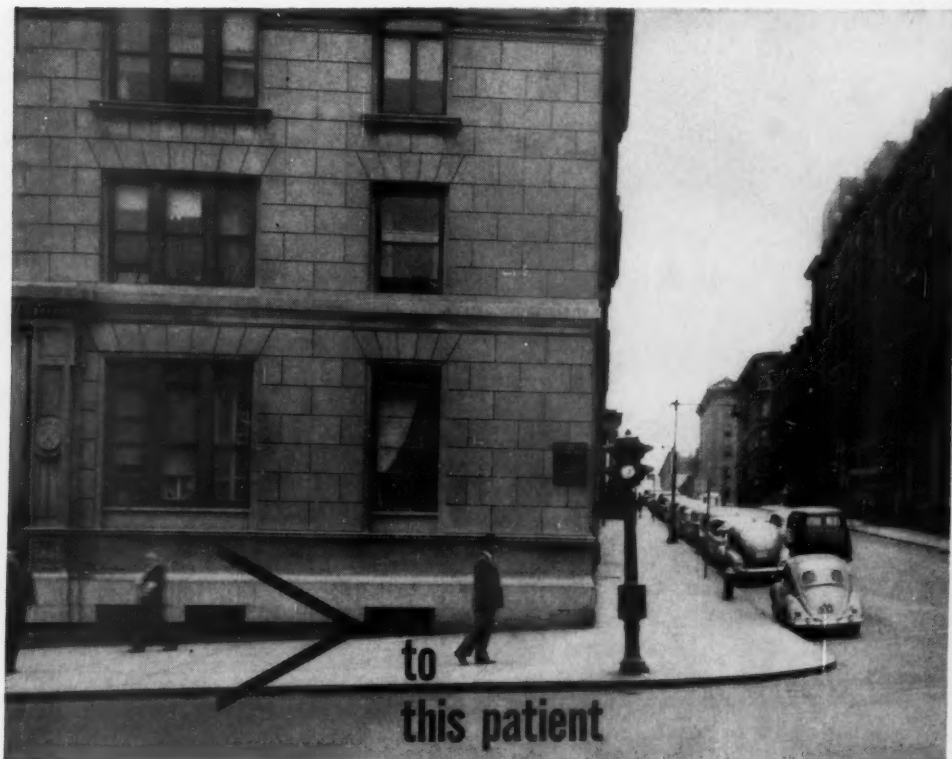
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**Nembutal\*** (Pentobarbital,  
Abbott)

\*Covers any degree of cerebral depression  
—from mild sedation to deep hypnosis.





**with intermittent claudication  
every block was a mile long**

now... **arlidin**

**makes the blocks so much shorter...  
he can walk many more of them in comfort**

Arlidin is available in 6 mg. scored tablets, and 5 mg. per cc. parenteral solution. See PDR for dosage and packaging.

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safely increases local blood supply and oxygen  
where needed most . . . in distressed "walking" muscles  
for sustained, gratifying relief of pain and spasm in

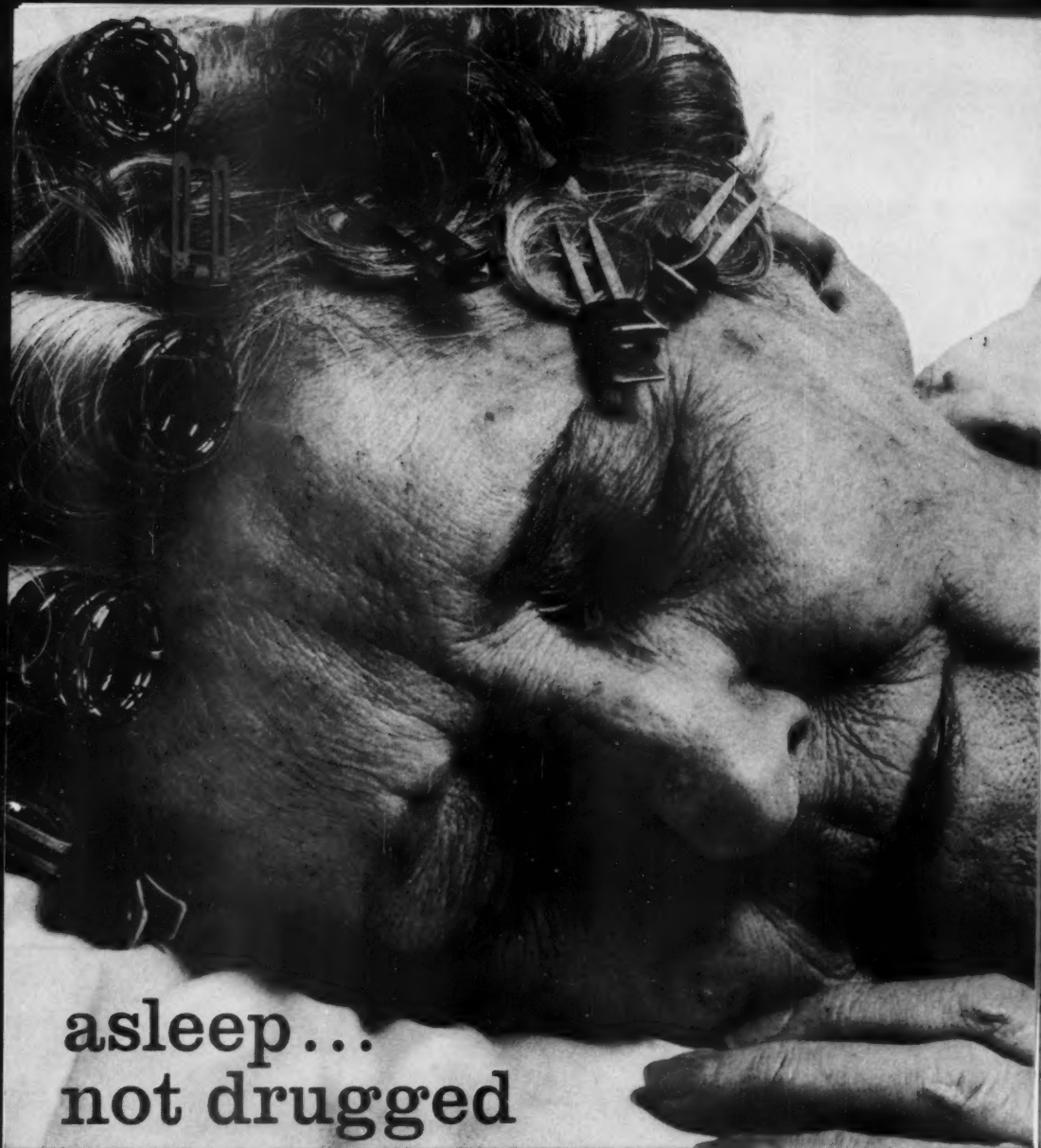
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*Relief? Certainly.*

*But, what about the atonic bowel?*

## **MODANE** *for both!*

Consider the task . . . Usually it is more than just moving fecal matter. Often, the atonic bowel cries for rehabilitation! MODANE answers both needs.

### **FOR ONE HALF OF THE PROBLEM**

MODANE provides Danthron—non-irritating, non-habit-forming, overnight de-constipant which acts gently, positively, on the large bowel only.

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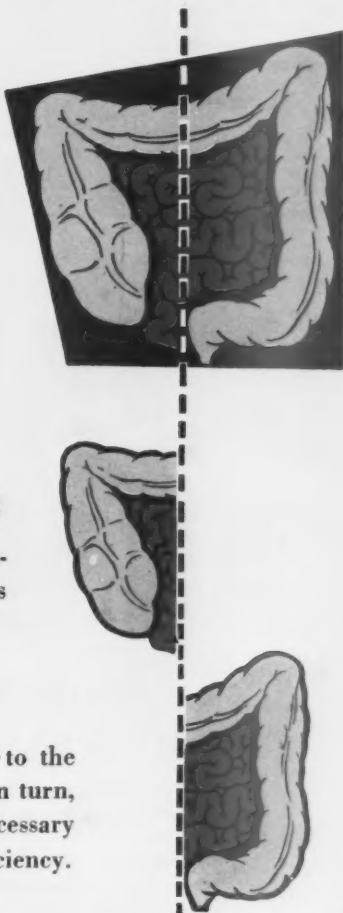
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1. Selzer, A. and Ryland, D.A.: COUNCIL ON DRUGS, Report to Council J.A.M.A. 168:762, (Oct. 11) 1958.



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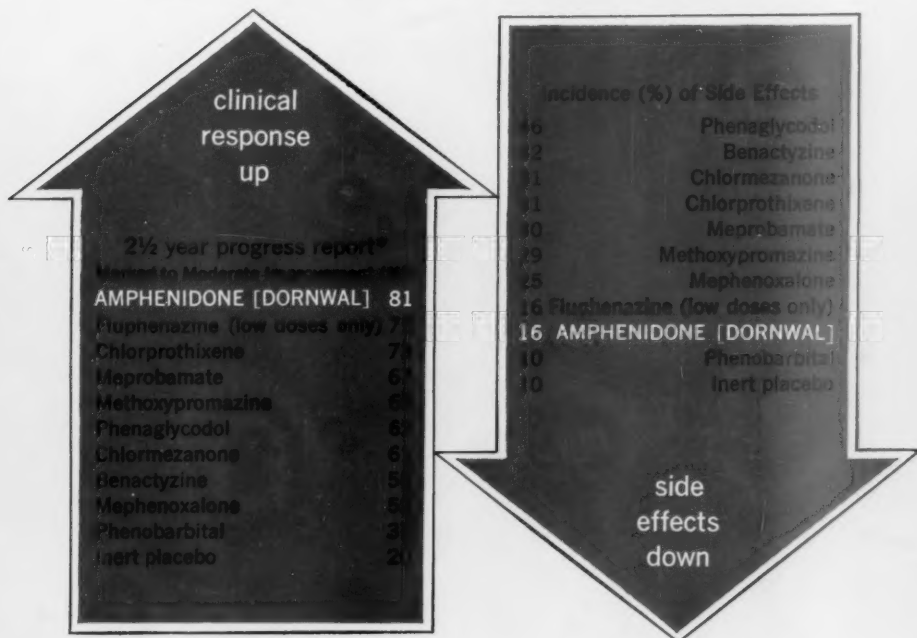
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\*Nodine, J. H.; Bodi, T.; Slap, J.; Levy, H. A., and Siegler, P. E.: Human bioassay of tranquilizers in psychosomatic disorders, Scientific Exhibit, American Medical Association Annual Meeting, Miami Beach, Florida, June 13-17, 1960.

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relaxes muscle tension

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"...continuous satisfactory control of the patient's painful state..."<sup>1</sup>

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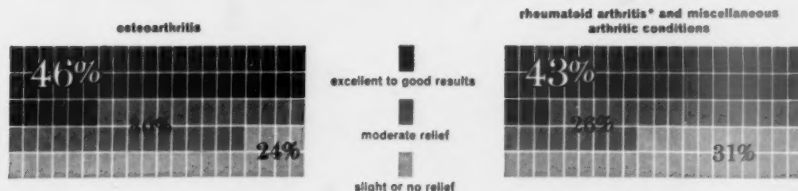
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"The resultant analgesia occurred promptly and persisted for at least 3 or 4 hours."<sup>8</sup>



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**References:** 1. Batterman, R. C., et al.: Am. J. Med. Sc. 238:315, 1959. 2. O'Dell, T. B.: Ann. New York Acad. Sc. 86:191, 1960. 3. O'Dell, T. B., et al.: J. Pharmacol. & Exper. Therap. 128:65, 1960. 4. O'Dell, T. B., et al.: Fed. Proc. 18:1694, 1959. 5. Gray, A. P., et al.: J. Am. Chem. Soc. 87:4347, 1965. 6. Wainer, A. S.: Ann. New York Acad. Sc. 86:250, 1960. 7. Clinical data from the files of the Medical Department, Irwin, Neisler & Co., 1959, 1960. 8. Batterman, R. C.: Ann. New York Acad. Sc. 86:203, 1960.

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for muscle relaxation plus analgesia

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McNeil Laboratories, Inc.  
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prescribe PARAFON in low back pain—sprains—  
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Each PARAFON tablet contains:

PARAFLEX® Chlorzoxazone† ..... 125 mg.

The low dosage skeletal muscle relaxant

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The superior analgesic in musculoskeletal pain

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*Precautions:* The precautions and contraindications  
that apply to all steroids should be kept in mind  
when prescribing PARAFON with Prednisolone.

\*tailman on hook-and-ladder fire engine

†U.S. Patent No. 2,895,877

31660



# "Are the xanthines effective in ANGINA PECTORIS?"

(Abstract of the paper with above title)

A favorable response was unequivocally demonstrated with aminophylline when administered intravenously to angina pectoris patients. In sharp contrast the author, noted for his original contributions to cardiovascular research, found oral administration ineffective in all patients tested. This suggested that the failure was correlated with sub-threshold theophylline blood-levels obtained with oral administration.

A 20% alcohol-solution of theophylline (Elixophyllin®) has been shown to provide blood levels comparable to those obtained with I.V. administration of aminophylline. This oral preparation and a placebo (identical in appearance, taste and alcoholic con-

tent) were tested by the electrocardiographic response obtained and by a double-blind clinical evaluation.

The author reported: "In the light of these findings, conclusions derived from animal experiments which have classed theophylline as a 'malignant' coronary vasodilator must be rejected for man." Elixophyllin administered orally to 30 patients was effective "not only in control of symptoms but in its modifying action on the electrocardiographic response to standard exercise. The efficacy of this preparation is based on the rapid absorption and attainment of high blood levels made possible by the vehicle employed."

(Russek, H. I., Am. J. Med. Sc. Feb., 1960)

## CLINICAL REFERENCE DATA ON

## ELIXOPHYLLIN®

**FORMULA:** A hydro-alcoholic solution of theophylline. Each 15 cc. (1 tablespoonful) contains 80 mg. theophylline (equivalent to 100 mg. aminophylline) and 20% ethyl alcohol.

**ORAL DOSAGE:** **First 2 days**—doses of 45 cc. t.i.d. (before breakfast, at 3 P.M., and on retiring).  
**Thereafter**—doses of 30 cc. t.i.d. (at same times).

**AVAILABLE:** Prescription only; bottles of 16 fl. oz. and 1 gallon.

**SPECIAL REPRINT:** Reprint of Dr. Russek's paper abstracted above on request.

*Sherman Laboratories*

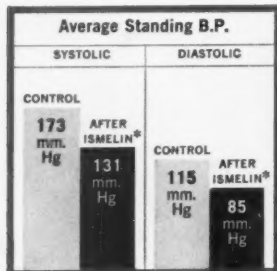
Detroit 11, Michigan

## ISMELIN® reduces high blood pressure to

According to reports from more than 100 clinical investigators, Ismelin—in moderate to severe hypertension—reduces blood pressure levels to normal or near-normal in a remarkably high percentage of patients. Following are summaries of typical findings

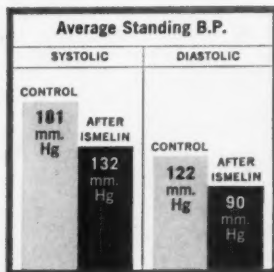
17 of 18 patients (94.4%) treated with Ismelin become normotensive in the erect position. Page and Dustan<sup>1</sup> gave Ismelin orally, alone or in combination with other antihypertensive drugs, to 18 patients daily for 2 to 10 weeks.

**RESULTS:** All 18 patients had reductions in standing blood pressure; 16 had moderate reductions in supine blood pressure as well. In 17 of the 18 cases, blood pressure levels became normal or near-normal in the erect position.



\*During last week of treatment.

In 14 of 15 patients (93.3%) on Ismelin, blood pressure reduced to normal or near-normal levels in the standing position. Ismelin was administered orally by Frohlich and Freis<sup>2</sup> for 4 to 9 weeks to 15 male patients selected from the hypertensive clinic.

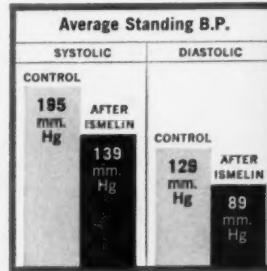


**RESULTS:** Ismelin evoked a potent antihypertensive response in the erect position: the blood pressure of 14 of the 15 patients dropped to normotensive or near-normotensive levels.

"The response [to Ismelin] was

characterized by a potent, orthostatic, antihypertensive effect similar to that seen with the ganglionic blocking drugs but without the side-effects of parasympathetic blockade."<sup>2</sup>

In 15 of 18 subjects (83.3%), guanethidine [Ismelin] reduced high blood pressure to near-normotensive levels. Guanethidine [Ismelin] was administered orally by Richardson and Wyso<sup>3</sup> to 18 male hospitalized patients with hypertension.



**References:** 1. Page, I. M., and Dustan, H. P.: J.A.M.A. 170:1285 (July 11) 1959. 2. Frohlich, E. D., and Freis, E. D.: M. Ann. District of Columbia 28:419 (Aug.) 1959. 3. Richardson, D. W., and Wyso, E. M.: Virginia M. Month. 46:377 (July) 1959. 4. Brest, A. N., and Moyer, J. H.: J.A.M.A. 172:104 (March 5) 1960. 5. Page, I. H.: Postgrad. Med. 27:448 (April) 1960. 6. Kirkendall, W. M., Flitz, A. M., Van Hecke, D. C., Wilson, W. R., and Armstrong, M. L.: Paper presented at a Symposium on Guanethidine (Ismelin), The University of Tennessee College of Medicine, Memphis, Tenn. April 22, 1960. 7. Leishman, A. W. D., Matthews, H. L., and Smith, A. J.: Lancet 2:1044 (Dec. 12) 1959. **Additional References:** 8. Brest, A. N., Duarte, C., Glantz, G., and Moyer, J. H.: Current Therap. Res. 2:17 (Jan.) 1960. 9. Maxwell, R. A., Mull, R. P., and Plummer, A. J.: Experientia 15:267 (July 15) 1959. 10. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. I.: J. Pharmacol. & Exper. Therap. 128:22 (Jan.) 1960. 11. Maxwell, R. A., Plummer, A. J., Schneider, F., Povalski, H., and Daniel, A. I.: Pharmacologist 1:68 (Fall) 1959. 12. Sheppard, H., and Zimmerman, J.: Pharmacologist 1:69 (Fall) 1959.



## *near-normal levels in 80 to 90% of cases<sup>1-3</sup>*

RESULTS: "All patients showed definite reduction in blood pressure coincident with administration of [Ismelin]. In most of the subjects [15] standing blood pressure could be maintained near normal levels."<sup>3</sup>

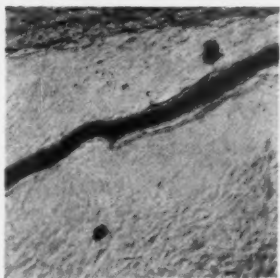
"Side-effects encountered... have indeed been minimal..."<sup>4</sup> Brest and Moyer<sup>4</sup> state: "Side-effects [of Ismelin] encountered to date have indeed been minimal, with mild diarrhea as the only significant complaint even when large daily doses (450 mg.) of the drug are administered. No evidence of toxic action of the drug has been encountered thus far." Page<sup>5</sup> observes: "...Guanethidine [Ismelin] has the advantage [over ganglionic blockers] in that it is much easier to handle and does not produce nearly as much dose sensitivity. Too much of a ganglion-blocking agent will really 'clobber' the patient; with Guanethidine, there is much more leeway." Kirkendall and co-workers<sup>6</sup> report: "Guanethidine has remarkably few side effects. The absence of symptoms of parasympathetic blockade makes its use better tolerated by most patients than conventional ganglion blocking therapy." Leishman and associates<sup>7</sup> conclude: "The capacity of guanethidine to reduce the blood-pressure of hypertensive patients



### **Ismelin Increases Arteriole Caliber**

Ismelin represents a new principle in the treatment of high blood pressure: It acts at the nerve-arteriole junction where it apparently opposes the release and/or distribution of the pressor substance, norepinephrine. Ismelin is not a ganglionic blocker.

◀ **BEFORE ISMELIN:** Photo shows normal arteriole in rat mesentery. (100x)



◀ **AFTER ISMELIN:** Ismelin has blocked the constricting influence of norepinephrine. Arteriolar caliber has significantly increased, while an adjacent capillary has filled. (100x)

Because it acts at the nerve-arteriole junction—with no demonstrable central or ganglion blocking effect—Ismelin produces a clear-cut antihypertensive response in a high percentage of cases.

without symptoms of parasympathetic blockade is consistent with a mechanism of selective sympathetic-nerve inhibition..."

*For complete information on precautions, dosage, and side effects, write to Medical Service Division, CIBA, Summit, New Jersey.*

Supplied: ISMELIN Tablets, 10 mg: (yellow, scored) and 25 mg. (white, scored); bottles of 100.

ISMELIN® sulfate (guanethidine sulfate CIBA)



in pain, such as that of cancer, **Thorazine®**,  
brand of chlorpromazine  
one of the fundamental drugs in medicine, reduces by potentiation the amount of narcotic needed; alleviates the anxiety that intensifies suffering; improves the patient's mental outlook. Also, controls nausea and vomiting.



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## CLINICAL NOTES

### HEMATOLOGY

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**PROPERTIES** ASTRAFER® I.V. is a neutral solution and does not irritate the intima. It is relatively free from the side reactions previously encountered with other intravenous iron preparations. 70-100% of the iron supplied by this agent is utilized in hemoglobin synthesis. Patient improvement is marked by a measurable sense of well being, and is seen coincidentally with the return to normal of serum iron and hemoglobin levels, usually beginning with the third or fourth injection.

**INDICATIONS** Severe iron deficiency anemia characteristic of late pregnancy and massive or repeated blood loss, where rapid replenishment of large iron deficits is mandatory, and wherever orally administered iron may be either ineffective or poorly tolerated. To date, there is no evidence that this agent is of any value in anemias of polyarthritis or chronic nephritis. **CONTRAINDICATIONS** are pernicious anemia, leukemia or bone marrow depression, and liver damage.

**DOSAGE** Initially, 1.5 cc. (30 mg.) to be administered slowly via the intravenous route. Patient should rest 15-30 minutes after each injection. Subsequent dosage increased according to instructions found in literature \* accompanying each package.

**SUPPLIED** 5 cc. color-break ampules, boxes of 10

## ASTRAFER® (ASTRA) I.V.

\*Further information including clinical background and detailed dosage instructions available to physicians on request.

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Three major criteria for an effective laxative have been established by physicians\*

*1. freedom from griping or other irritating side effects*

*2. clinically proven effectiveness*

*3. predictable action*

\*Results of a survey of over 1,000 physicians conducted by the Bureau of Research, Inc., 555 W. Jackson Blvd., Chicago 6, Illinois (April, 1960).

# PERI-COLACE<sup>®</sup>

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meets physicians' criteria  
for an effective laxative

▶ With Peri-Colace "...side effects such as griping are reduced to a minimum."<sup>1</sup>

▶ Peri-Colace, a unique combination of Peristim<sup>®</sup> and Colace<sup>®</sup> (dioctyl sodium sulfosuccinate) "...gave satisfactory results in 97 per cent of the cases [130 hospitalized patients]."<sup>2</sup>

▶ You can depend on Peri-Colace—experience in practice has shown that it promptly, yet gently, induces bowel evacuation within 8 to 12 hours in most patients.

*References:* (1) Broders, A. C., Jr.: *Am. J. Digest. Dis.* 2:483-486 (Sept.) 1957. (2) Lamphier, T. A.: *Am. J. Proctol.* 8:442-444 (Dec.) 1957.



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Supplied: As 0.75 mg. and 0.5 mg. scored, pentagon-shaped tablets in bottles of 100. Also available as Injection DECADRON Phosphate. Additional information on DECADRON is available to physicians on request. DECADRON is a trademark of Merck & Co., Inc.

\*From a clinical investigator's report to Merck Sharp & Dohme.

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*gill*





# ANNALS OF INTERNAL MEDICINE

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VOLUME 53

NOVEMBER, 1960

NUMBER 5

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## IDIOPATHIC AND SECONDARY THROMBOCYTO- PENIC PURPURA: CLINICAL STUDY AND EVALUATION OF 381 CASES OVER A PERIOD OF 28 YEARS \*

By CHARLES A. DOAN, M.D., F.A.C.P., BERTHA A. BOURONCLE, M.D.,  
and BRUCE K. WISEMAN,† M.D., F.A.C.P., *Columbus, Ohio*

For the last 28 years we have been concerned with the study of thrombocytopenic purpura. Our spiraling interest has paralleled the progressive increase in the total number of patients with this syndrome seen in our Hematology Clinics in each five-year period (figure 1).

Until 1950 the only major effective therapeutic procedure available was splenectomy. Since then, corticosteroids have been selectively employed and recommended.

The purpose of this study is to present an evaluation of the clinical and hematologic findings in thrombocytopenic purpura; to establish a comparison of the results obtained with splenectomy versus corticosteroid therapy; to report the postsplenectomy life history of idiopathic thrombocytopenic purpura as a disease entity; to determine if the evidence supports the concept of a hypersusceptibility to lupus erythematosus or to virulent bacterial or viral infections in the postsplenectomy state; and to pinpoint those underlying constitutional diseases in which thrombocytopenic purpura is most commonly encountered as a secondary hypersplenic complication.

\* Received for publication June 6, 1960.

Presented at the Forty-first Annual Session of The American College of Physicians, San Francisco, California, April 7, 1960.

From the Hematology Division of the Medical Department, Ohio State University, Columbus.

† Deceased.

Requests for reprints should be addressed to Charles A. Doan, M.D., Dean, Director of the Health Center, The Ohio State University College of Medicine, 1645 Neil Avenue, Columbus 10, Ohio.

ADMISSIONS OF IDIOPATHIC AND  
SECONDARY THROMBOCYTOPENIC PURPURA  
PER FIVE YEAR PERIOD: 1931-1959

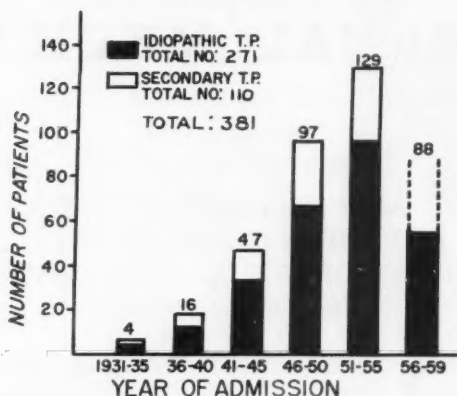


FIG. 1.

#### MATERIAL AND METHODS

A study of 381 cases of thrombocytopenic purpura, seen in the Hematology Division of the Medical Department at Ohio State University in the last 28 years, constitutes the material of this investigation. Of these patients, 271 were diagnosed as primary or idiopathic thrombocytopenic purpura, and 110 as secondary thrombocytopenic purpura.

By definition, we have considered as "idiopathic" those patients with thrombocytopenic purpura who did not have a viral or other precipitating infection prior to the initiation of the symptoms of thrombocytopenic purpura, and who had no other identifiable basic disease process; those in whom the histopathologic examination of the removed spleen did not reveal any other disease state; and, finally, those who, during their months and years of follow-up, failed to develop symptoms or signs of a progressive systemic disease. We considered as having "secondary" thrombocytopenic purpura those patients who, prior to the initiation of their symptoms, did have a history of a preceding upper respiratory infection or other viral infection, such as infectious mononucleosis, chickenpox, measles, etc.; those patients with a known basic disease process, such as Boeck's sarcoid, Gaucher's disease, one of the lymphomas, malignancy, etc.; those patients in whom the histopathologic specimen of the spleen revealed an abnormality compatible with a basic disease process; and those patients who subsequently developed a systemic disease, such as lupus erythematosus, during many months or years of follow-up.

We have followed and kept in touch with 93% of the patients with idiopathic thrombocytopenic purpura and with 97% of the patients with secondary thrombocytopenic purpura in this series through December, 1959, or until their deaths. This was accomplished in the majority of cases by the return of the patient to our laboratories for complete clinical and hematologic examinations; in some, by the excellent coöperation of the local referring physician in securing and supplying the desired data. In the evaluation of results of therapy we have eliminated the few patients who died before therapy could be initiated, or before it could have time to prove its effectiveness, as well as the 3% of patients with whom we lost contact.

The length of time of follow-up of patients with thrombocytopenic purpura is indicated in table 1.

TABLE 1  
Follow-up in Years of Patients with Idiopathic and Secondary  
Thrombocytopenic Purpura

Follow-up in Years	Per Cent of Patients
Less than 1	13.8
From 1 to 5	27.8
From 5 to 10	31.1
From 10 to 15	19.2
Over 15	8.1

The diagnosis of thrombocytopenic purpura was confirmed in all patients by supravital examination of the peripheral blood and bone marrow. The characteristic finding in the peripheral blood is thrombocytopenia. The characteristic finding in the bone marrow is a hyperplasia of young normal megakaryocytes actively fragmenting platelets with normal erythropoiesis and myelopoiesis. No cases of thrombocytopenic purpura have been included if the disease was thought to be an effect of an ingested drug or the result of exposure to an industrial toxin. Rare disorders such as thrombotic thrombocytopenic purpura were excluded.

## RESULTS

### IDIOPATHIC THROMBOCYTOPENIC PURPURA

The total number of patients in this group is 271. The distribution of patients with this disease, with reference to sex and age, is expressed in figure 2. The disease occurred predominantly in females (68%) as compared with males (32%). It is more common in male children under the age of 10, and progressively diminishes in frequency in this sex in the following decades of life. In the female its incidence is greater between the second and third decades of life, the most active childbearing period. It is of interest to note that 17 patients were over 60 years of age when the diagnosis of idiopathic thrombocytopenic purpura was first made.

The critical level for platelets in our laboratory is considered to be 50,000

### IDIOPATHIC THROMBOCYTOPENIC PURPURA

DISTRIBUTION OF PATIENTS WITH REFERENCE TO SEX AND AGE-

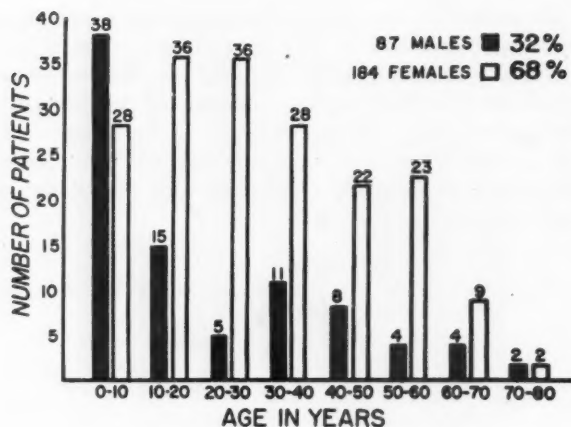


FIG. 2.

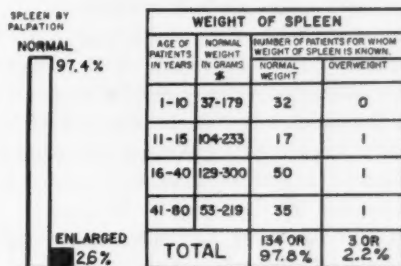
per cubic millimeter or below; 82% of the patients in this series showed platelet levels in this range on their first examination.

The most common presenting symptoms were purpura and ecchymoses. In 78 patients, these were the only presenting symptoms. In four patients, vaginal bleeding was the only presenting symptom. In the remaining 189 patients, purpura and/or ecchymoses were accompanied by one or several other sources of bleeding which, in order of frequency, were: epistaxis, bleeding gums, vaginal bleeding, gastrointestinal bleeding, and hematuria. Cerebral vascular accident was noted as one of the presenting symptoms in nine patients; four of these patients were between 14 and 50 years of age; the other five were over 50 years of age.

In the physical examination, 97.4% of the patients with idiopathic thrombocytopenic purpura showed a spleen of normal size; in only 2.6% was the spleen found to be enlarged by palpation. This clinical observation is corroborated by the actual weight of the spleen obtained at the time of splenectomy. Ninety-seven and eight tenths per cent of the spleens were within the normal weight range for the age of the patient according to the table of postmortem weights of the normal human spleen given by Krumbhaar and Lippincott<sup>1</sup> (figure 3).

*Results of Therapy:* Until 1950, the only major therapeutic procedure used was splenectomy. Since then, corticosteroids have been selectively employed. The results obtained are expressed in table 2.

# IDIOPATHIC THROMBOCYTOPENIC PURPURA SPLEEN SIZE AND WEIGHT



KRUNDHAR AND LIPPINCOTT

FIG. 3.

One hundred sixty-seven patients had splenectomy as the only therapy; of these, 157 had a prompt and satisfactory clinical and hematologic response, the platelets rapidly returning to normal levels, with disappearance of all symptoms of thrombocytopenic purpura. Ten patients failed to respond to splenectomy. Of these 157 patients, after follow-up, 15 had recurrence of their original symptoms: eight within one year, and three within one to five years after splenectomy; in four patients, the recurrences were associated with pregnancy. Hence, 85% of the total number of patients who had

TABLE 2  
Idiopathic Thrombocytopenic Purpura Response to Therapy

Therapy	Number of Patients Evaluated	Hematologic and Clinical Response	No Response	Recurrences			Good Response Without Recurrence
				With Pregnancy	Without Pregnancy	Unless Continuous Corticosteroid	
Splenectomy	167	157	10	4	11	—	85.0%
Splenectomy following corticosteroid failure	42	41	1	0	8	—	78.5%
Splenectomy within 7 days of initiation of corticosteroid	19	19	0	0	1	—	94.7%
Total number of splenectomies	228	217	11	4	20	—	84.6%
Corticosteroids	59	11	43	0	2	5	15.2%
Corticosteroid following splenectomy failure	4	1	1	0	0	2	25.0%
Total number on corticosteroids	63	12	44	0	2	7	15.8%

splenectomy as the only therapeutic procedure had a good response, without further recurrence of their symptoms.

The second group (42 patients) had splenectomy only after they failed to respond to an adequate trial of corticosteroid therapy over periods of from one month to three years. Forty-one of them had a hematologic and clinical response after splenectomy; only one failed to respond. In the subsequent follow-up, eight patients had recurrence of their symptoms unrelated to pregnancy. In our experience, favorable permanent results were obtained, after splenectomy, in 78.5% of patients who had failed to respond to corticosteroids.

The third group (19 patients) had splenectomy within seven days of initiation of corticosteroid therapy. This medication was discontinued shortly after surgery. It is difficult to evaluate the results of corticosteroids in this group of patients, but the remission of their symptoms and rapid increase in platelets obtained after splenectomy have persisted in 94.7% of the patients of this group.

In summary, 84.6% of patients with idiopathic thrombocytopenic purpura had complete and permanent relief from their symptoms after splenectomy. The surgical mortality was 1.4%.

Corticosteroid therapy alone was given to 59 patients. Eleven of these patients had a clinical and hematologic response, and 43 failed to respond. Of the 11 patients who responded to corticosteroids, two had a subsequent relapse of symptoms unrelated to pregnancy. Another five patients required continuous corticosteroid treatment to maintain an adequate remission.

We have considered the response to corticosteroids to be good when, after an adequate trial on this medication (one month to three years in our series), the platelet count returned to normal or adequate levels, and this remission continued in spite of progressive decrease and eventual discontinuance of the medication. In some patients, a decrease in the corticosteroid dosage was attempted two or three different times, only to be followed by a marked reduction in platelets, before the treatment was considered to be a failure.

We cannot accept as a satisfactory therapeutic result a temporary response to corticosteroids if, to maintain an adequate platelet level, continued steroid therapy is required indefinitely. The possible complications and disadvantages of this medication are well known: each patient must be observed carefully and constantly during therapy for such manifestations as rounding of the face, acne, osteoporosis, hyperglycemia, tendency to infections, activation of a dormant tuberculous process, bleeding peptic ulcer, mental disturbance, etc.

Four of the patients who failed to respond to splenectomy were treated with corticosteroids; one had a definite response, one had no response, and two required continuous therapy to maintain the remission. The results



in this small group of patients suggest that, when a patient fails to respond to splenectomy, corticosteroid therapy should be tried.

In summary, of 63 patients treated with corticosteroids, only 15.8% obtained a satisfactory and permanent response without recurrence or need of continued therapy.

It seems clear from an evaluation of these results that splenectomy remains the treatment of choice in idiopathic thrombocytopenic purpura. This is in agreement with recent reports from several other hematologic centers.<sup>2, 3</sup> Nevertheless, the superiority of splenectomy in this disease has been challenged by some investigators.<sup>4</sup> The possible disadvantages cited include:

1. The hazard of severe infection in splenectomized infants and children.<sup>5-7</sup>

In our group of patients with idiopathic thrombocytopenic purpura, a special effort has been made to follow and to establish the incidence of post-splenectomy infections with special reference to those most frequently men-

TABLE 3  
Idiopathic Thrombocytopenic Purpura. Incidence of Infections After  
Splenectomy; only 1.2%

	Under One Year of Age	1-10 Years of Age	Over 10 Years of Age
Number of patients	2	60	173
Pneumonia (non-fatal)	0	0	3
(fatal)	0	0	0
Septicemia	0	0	0
Meningitis	0	0	0
Tuberculosis	0	0	0

tioned: pneumonia, septicemia, meningitis and tuberculosis. Only three patients, who were over 10 years of age at the time of splenectomy, contracted a major infection (pneumonia) later on; each recovered after proper medical therapy. This makes a total of only 1.2% of serious infections in the group that was operated upon and that was followed over a period of years. Our experience does not support the contention of increased incidence of fatal infections after splenectomy in the age group of patients who develop idiopathic thrombocytopenic purpura (table 3). These results are in agreement with reports from other investigators.<sup>8-10</sup>

In a further attempt to study both the quantitative and the qualitative immunologic response of splenectomized patients to bacterial antigens, 47 patients with surgically reversed idiopathic thrombocytopenic purpura and 10 patients with corrected secondary thrombocytopenic purpura were tested for their ability to form specific antibodies in the absence of the spleen. As antigen, one to three injections of the Foshay heat-killed tularemia vaccine were given. Normal titers of specific antibodies were induced promptly in 45 of the 47 patients (table 4).<sup>11</sup>

TABLE 4  
Idiopathic and Secondary Thrombocytopenic Purpura Antibody Response  
After Splenectomy

Diagnosis	Total Number of Patients	Patients Forming Antibodies	Patients not Forming Antibodies
Primary thrombocytopenic purpura	37	35	2
Secondary thrombocytopenic purpura	10	10	0
Totals	47	45	2

2. The other claim against the superiority of splenectomy is the strong possibility of dissemination of the lupus erythematosus process following splenectomy.<sup>12, 13</sup>

We have searched carefully for this development in our patients. We first established the incidence of lupus erythematosus in the general University Hospital admissions. We have included only patients admitted from January 1, 1950, to December 31, 1959, since it is only during this period that an accurate diagnosis of lupus erythematosus has been possible. The total number of patients admitted to the University Hospital in this period was 132,235. Among these patients, 76 (0.06%) had the diagnosis of lupus erythematosus confirmed. Five of these had concomitant symptoms of thrombocytopenic purpura.

During the same period of time, 243 patients were diagnosed as having thrombocytopenic purpura. In only five of these patients was the diagnosis of lupus erythematosus confirmed; in two of them the thrombocytopenic purpura was an initial finding of the lupus erythematosus syndrome. Both patients died as a consequence of bleeding. The other three patients were originally diagnosed as uncomplicated idiopathic thrombocytopenic purpura; the symptoms of lupus erythematosus developed four, five and eight years, respectively, after successful splenectomy. All three of these patients are alive at present, have normal platelets, and their symptoms of lupus erythematosus are under control on corticosteroid therapy.

TABLE 5  
Thrombocytopenic Purpura and Systemic Lupus Erythematosus

	Total Number of Patients	Lupus Erythematosus Disseminatus
Incidence of L.E. per general hospital admissions (January 1, 1950 to December 31, 1959)	132,235	{ With thrombocytopenic purpura: 5 { Without thrombocytopenic purpura: 71 { Total number of L.E.: 76 or 0.06%
Incidence of L.E. in patients having thrombocytopenic purpura (January 1, 1950 to December 31, 1959)	243	{ Initial finding (no splenectomy): 2 or 0.8% { Post-splenectomy: 3 or 1.2% { Total number of L.E.: 5 or 2.0%

From the above statistics it may be noted that the incidence of lupus erythematosus appears to be higher in patients with thrombocytopenic purpura than in general admissions to the hospital. However, this incidence is 2%, and only 1.2% after splenectomy (table 5).

Splenectomy did not precipitate or stimulate the dissemination of symptoms or signs of lupus erythematosus in any of the three patients. We do not believe that splenectomy should be withheld in any patient with idiopathic thrombocytopenic purpura for fear of precipitating or disseminating an improbable case of lupus erythematosus.

Our pathologists have reviewed the histopathologic sections of the spleen of our patients diagnosed as having idiopathic thrombocytopenic purpura at the time of surgery. They have found none of the characteristic changes of lupus erythematosus. Sections of all spleens available have been reviewed again specifically by Dr. Jacob Old, of the Department of Pathology, who agrees with the original observations.

In 13 cases, the preoperative diagnosis of idiopathic thrombocytopenic purpura was changed to secondary thrombocytopenic purpura after the histopathologic examination of the spleen revealed tuberculosis in five patients, Hodgkin's disease in three patients, Boeck's sarcoid in three patients, histoplasmosis in one patient, and giant follicular lymphoma in one patient. Splenectomy not only promptly corrected all signs and symptoms of thrombocytopenic purpura in these patients, but also provided us with the unsuspected basic diagnosis. These results further substantiate the superiority of splenectomy over corticosteroid therapy. Especially in the five patients with tuberculosis of the spleen, corticosteroid therapy might have activated and disseminated the tuberculous process even further.

Another advantage of splenectomy over corticosteroid therapy is the immediacy of the hematologic response. In 82.1% of the patients who responded to splenectomy, the platelets markedly increased, usually as soon as the splenic pedicle was ligated, or at least within the first 24 hours; in

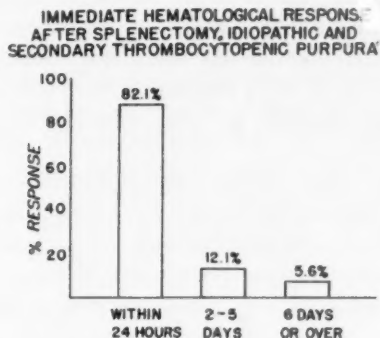


FIG. 4.

12.1%, within two to five days; in only 5.6% of the cases have we observed a greater delay in platelet response. With corticosteroids the response is usually seen only after six or more days. The patient is highly susceptible to cerebral or other dangerous hemorrhage while waiting for the platelet count to rise (figure 4).

It has been suggested that patients with idiopathic thrombocytopenic purpura should be prepared for splenectomy with corticosteroid therapy. In our series, however, the incidence of nonfatal, postsurgical complications in thrombocytopenic purpura has been 23.6% in patients who had corticosteroids prior to splenectomy, and only 9.4% in patients who had splenectomy as the only therapy (table 6). The complications included subphrenic abscess, infected ulcer, thrombophlebitis, miscellaneous infections, subphrenic hematoma, pleural effusion, atelectasis, etc.

TABLE 6  
Idiopathic and Secondary Thrombocytopenic Purpura Post-Surgical Complications

Disease	Splenectomy Only		Splenectomy plus Corticosteroids	
	Number of Patients	Complications	Number of Patients	Complications
Idiopathic thrombocytopenic purpura	163	17	61	15
Secondary thrombocytopenic purpura	49	3	11	2
Total	212	9.4%	72	23.6%

*Pregnancy and Idiopathic Thrombocytopenic Purpura:* Purpura complicating pregnancy has been reported not infrequently since the original account by Barnes in 1867.<sup>14-19</sup> It is interesting to remark the incidence of idiopathic thrombocytopenic purpura associated with pregnancy in this series of patients. The first symptoms of thrombocytopenic purpura developed during pregnancy in 18 patients of our series. Five of these patients had successful splenectomy during the course of pregnancy. Two patients were treated with corticosteroids: one has required continuous therapy up to the present time, with a total of 14 months of treatment, while the other one failed to respond satisfactorily to corticosteroids, but later responded to splenectomy.

In 11 patients the symptoms and signs of thrombocytopenic purpura continued after the completion of pregnancy. Seven patients had splenectomy six weeks, two patients four months, and two patients 10 and 12 months after delivery. All had a good response to splenectomy. Only one was treated with corticosteroids after the completion of pregnancy, with satisfactory control.

Four splenectomized patients had recurrence of their symptoms during

pregnancy, one patient with one pregnancy, and the other three with three consecutive pregnancies.

Six of the children born to mothers having idiopathic thrombocytopenic purpura had congenital thrombocytopenic purpura. Three of them went into remission spontaneously; two were treated with corticosteroids, and one required splenectomy at the age of four weeks. This child started having massive gastrointestinal bleeding, and splenectomy was considered to be mandatory. He had an immediate recovery, and is at present a healthy eight year old boy.

The status of patients with idiopathic thrombocytopenic purpura as of December, 1959, is summarized in table 7. Of 271 patients, 83.1% are living and free of all idiopathic thrombocytopenic purpura symptoms, and 3.3% are living with some continuing symptoms. The surgical mortality (within 24 hours) was 1.4%. Subsequently, 4.4% died from idiopathic

TABLE 7

Status of Patients with Idiopathic Thrombocytopenic Purpura as of December 1959

Total Number of Patients	Living and Free of Symptoms	Living with Symptoms	Surgical Mortality	Died		Followed to 1959 or Death	Partially Followed Up	Loss of Follow Up
				With I.T.P.	Other Causes			
271	83.1%	3.3%	1.4%	4.4%	4.7%	93%	4%	3%

thrombocytopenic purpura, and 4.7% from causes unrelated to idiopathic thrombocytopenic purpura. We have successfully followed 93% of these patients to December, 1959, or until their deaths; we have also partially followed 4%, and have failed to follow only 3% of all patients in this series.

#### SECONDARY THROMBOCYTOPENIC PURPURA

One hundred ten patients in our series were classified as having secondary thrombocytopenic purpura. The distribution of patients according to age and underlying disease is tabulated in table 8. Fifty-seven of these patients had a history of a viral infection prior to the initiation of the purpuric symptoms. Forty-two of them were children under 12 years of age. The most common infections associated with the development of thrombocytopenic purpura in our series were an upper respiratory infection (21 patients), measles (16), infectious mononucleosis (11), chickenpox (five), mumps (three), and infectious hepatitis (one). A similar associated incidence has been reported from other clinics.<sup>20-23</sup>

The symptoms and signs of thrombocytopenic purpura usually developed from one to three weeks after the initiation of the underlying infection, and usually when the patients were in the convalescent period of their basic illness.

TABLE 8  
Secondary Thrombocytopenic Purpura. Distribution of Patients According to Basic Disease and Age

Disease	Age in Years			Total
	0-12	12-30	Over 30	
Viral infections	42	12	3	57
Tuberculosis	5	4	2	11
Lymphomas	2	1	5	8
Leukemias	1	0	5	6
Gaucher's disease	1	3	1	5
Boeck's sarcoid	1	3	1	5
Systemic lupus erythematosus	0	2	3	5
Others (misc.)	4	2	7	13
Totals	56	27	27	110

Eleven patients in this group of secondary thrombocytopenic purpura were found to have tuberculosis. (In five of them the tuberculous process was found at the time of the pathologic examination of the removed spleen. Five patients had concomitant pulmonary tuberculosis, and one had tuberculous peritonitis and salpingitis.) A review by Kalinowski and Walker of thrombocytopenic purpura in tuberculosis in 32 cases from the medical literature and two patients of their own has been published in the British literature.<sup>24</sup>

In eight patients the underlying disease was a lymphoma (four had Hodgkin's disease, two had lymphosarcoma, and two had giant follicular lymphoblastoma).

Six patients had chronic leukemia (lymphatic, monocytic and/or leukemic reticuloendotheliosis), five had Gaucher's disease, five had Boeck's sarcoid, five had or later developed systemic lupus erythematosus, and 13

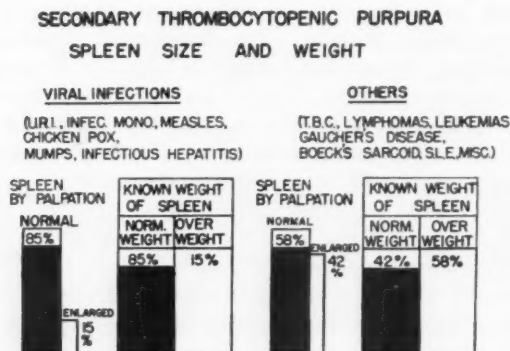


FIG. 5.



TABLE 9  
Secondary Thrombocytopenic Purpura Response to Therapy

Therapy	Number of Patients Evaluated	Hematologic and Clinical Response	No Response	Recurrences			Good Response Without Recurrence
				With Pregnancy	Without Pregnancy	Unless Continuous Corticosteroid	
Splenectomy	48	48	0	1	5	—	87.5%
Splenectomy following corticosteroid failure	8	8	0	0	1	—	87.5%
Splenectomy within 7 days of initiation of corticosteroids	3	3	0	0	2	—	
Total number of splenectomies	59	59	0	1	8	—	84.7%
Corticosteroids	36	24	9	0	1	3	63.8%

had other miscellaneous diseases involving the spleen, such as histoplasmosis, scarlet fever, syphilis, Mediterranean anemia, etc.

The range of spleen size in the group of patients with secondary thrombocytopenic purpura is expressed in figure 5. In the 57 patients with purpura secondary to viral infections, the spleen was normal by palpation as well as by actual weight of the excised spleen in 85% of the patients. In the other groups, including the lymphomas, the leukemias, tuberculosis, Gaucher's disease, Boeck's sarcoid, Mediterranean anemia, etc., the spleen was enlarged by palpation in 42% and enlarged by actual weight of the removed spleens in 58%.

The response to therapy in this heterogeneous group of diseases, all with the one common denominator of splenic involvement and secondary thrombocytopenic purpura, is expressed in table 9. Of 59 patients treated by splenectomy, 84.7% had a complete and permanent reversal of the thrombocytopenia. Of 36 patients treated with corticosteroids, 63.8% had a complete and permanent recovery.

Thus, the results with corticosteroids in secondary thrombocytopenic purpura are significantly better, and parallel more closely those obtained from splenectomy.

This is particularly true in the group of purpuras occurring after post-viral infections. The thrombocytopenic purpura secondary to viral infections (upper respiratory infection, measles, infectious mononucleosis, chickenpox, mumps, etc.) is usually transitory. In most cases a spontaneous remission may be expected. Until 1950 we observed these patients closely, using supportive fresh whole blood transfusions; splenectomy was done only if the bleeding was severe and persistent enough to endanger the life of the patient.

Since 1950 we have preferred to treat cautiously with corticosteroid therapy any patient with secondary thrombocytopenic purpura due to viral infection. We have reserved splenectomy for those cases failing to respond to or to tolerate this medication. Only five of 36 patients treated with corticosteroids in this group failed to respond to an adequate trial of this medication and required splenectomy for permanent control.

Spontaneous remissions are not uncommon in these postinfectious secondary thrombocytopenic purpuras; this was the case in 17 patients of our series.

In the other types of secondary thrombocytopenic purpura, such as Boeck's sarcoid, Gaucher's disease, tuberculosis, Mediterranean anemia, and selected cases of lymphomas and the leukemias, we still believe that splenectomy is the treatment of choice, and that further appropriate specific treatment is frequently more effective following the removal of a large splenic focus of disease than before.

#### SUMMARY AND CONCLUSIONS

From our experience with 381 patients with thrombocytopenic purpura studied over the last 28 years, we believe that:

1. Splenectomy remains the treatment of choice in patients with primary or idiopathic thrombocytopenic purpura, as well as in many selected patients with secondary thrombocytopenic purpura.

In our hands splenectomy has resulted in more prompt remissions and more permanent recoveries with fewer complications than with any other therapy.

2. Corticosteroid therapy should be reserved for selected patients:

- (a) Children or young adults with thrombocytopenic purpura secondary to transitory viral or infectious diseases.
- (b) Any patient with cardiac or other complications contraindicating surgery.
- (c) Patients failing to respond to splenectomy, or having recurrence of their symptoms after splenectomy, if accessory splenic tissue can be ruled out.

3. There is no evidence in this group of patients that splenectomy increased their susceptibility to subsequent infections, and both cellular and specific globulin antibody responses have been shown to be prompt and adequate.

4. The incidence of lupus erythematosus disseminatus has been 2% in this series of patients with thrombocytopenic purpura, and 0.06% in the general admissions to the hospital over the last decade. Splenectomy did not, however, precipitate or disseminate the symptoms or signs of lupus erythematosus in any of our patients, and in our experience the hazards to life

during an acute hypersplenic thrombocytopenic crisis far outweigh the dangers of developing a subsequent delayed lupus erythematosus syndrome in these patients.

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For the inclusion of their patients, to Dr. Henry E. Wilson and Dr. Robert L. Wall, from the Hematology Division, Department of Medicine, The Ohio State University. For assistance in collecting some of the data, to Dr. H. Davidson, Dr. N. Bellios, Dr. R. Stuart and Dr. G. Abels, all graduates of The Ohio State University.

#### SUMMARY IN INTERLINGUA

Iste studio presenta un evaluation del constataciones clinic e hematologic in 381 pacientes con purpura thrombocytopenic. Inter iste pacientes, 271 esseva diagnosticate como suffrente de primari o idiopathic purpura thrombocytopenic. In 100 le diagnose esseva secundari purpura thrombocytopenic. Le major punctos evalutate in le presente studio es: Un comparison del resultados obtenite per splenectomy con illos obtenite per therapia corticosteroide; le historia vital post splenectomy in idiopathic purpura thrombocytopenic como entitate pathologic; le studio de susceptibilitate pro infectiones post splenectomy; le evaluation de symptommas de lupus erythematosus post splenectomy; e le precisisation del subjacente morbos constitutional in que purpura thrombocytopenic es incontrate le plus communmente como complication hypersplenic secundari.

Super le base de nostre experientias nos opina que splenectomy remane le therapia de election in pacientes con primari o idiopathic purpura thrombocytopenic e etiam in multe seligite pacientes in qui le purpura thrombocytopenic es secundari.

Therapia a corticosteroides deberea esser reservate pro juveniles o juvene adultos con purpura thrombocytopenic secundari a transiente morbos infectiose o viral, pro pacientes in qui complicationes cardiac o altere rende le intervention chirurgic contraindicate, e pro pacientes qui non responde al splenectomy o qui manifesta recurrentias del symptommas post le splenectomy.

In le presente gruppo de pacientes, nihil indicava que splenectomy augmenta le subsequente susceptibilitate pro infectiones. Le responsas de anticorpore, tanto cellular como etiam specific, esseva normal.

Le incidentia de disseminate lupus erythematosus in iste serie de pacientes con purpura thrombocytopenic esseva 2% pro le complete periodo de dece annos. In le population general de nostre hospital le correspondent valor es 0,06%. Tamen, splenectomy non precipitava e non disseminava le symptommas e signos de lupus erythematosus in ulle de nostre pacientes. In nostre opinion, le riscos mortal de un acute crise de thrombocytopenia hypersplenic excede per multo le periculo del subsequente disveloppamento de un tardive syndrome de lupus erythematosus.

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## LYMPHOSARCOMA: THE EFFECTS OF THERAPY AND SURVIVAL IN 1,269 PATIENTS IN A RE- VIEW OF 30 YEARS' EXPERIENCE \* †

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### INTRODUCTION

A REVIEW has been completed of the experience with lymphosarcoma at the Memorial Center for Cancer and Allied Diseases during the last 30 years. This has been a comprehensive study, the details of which appear elsewhere.<sup>1</sup> This report summarizes the information obtained from this analysis as it pertains to the age and sex distribution of the group, the histologic classification, transitions of the disease to leukemia, the results and complications of therapy, and the prognosis and survival of various subgroups.

### CASE SELECTION

The study includes all cases where the probable clinical onset of disease occurred from 1928 through 1952. Records were analyzed as of January 1, 1958, thus providing at least a five-year period of follow-up.

No case was acceptable for review unless the diagnosis was considered to be definite on tissue examination by a senior member of the Pathology Department of the Memorial Center. Doubtful cases were reviewed by Dr. John Berg and Dr. Stephen Sternberg.

An attempt was made to exclude all patients with manifest leukemia when they were first seen at this institution. Unfortunately, this must be done on largely arbitrary criteria, often seeming vague, but of definite importance in directing therapy. Cases where the initial blood picture showed more than 30,000 white blood cells per cubic millimeter, with greater than 70% lymphocytes or immature cells, were excluded as being probably leukemic if no bone marrow examination was done. Cases where a bone marrow examination early in the course of the disease showed extensive replacement by lymphocytic or immature cells were also excluded as being probably

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leukemic, even if the peripheral blood appeared to be normal. Occasionally, bone marrow on aspiration or at postmortem examination revealed accumulations of cells thought to be characteristic of lymphosarcoma cells.<sup>2</sup> These patients frequently had intermittent or minor manifestations in the peripheral blood. Such cases were included in this study and given the hybrid name of leukolymphosarcoma.

Frequently the hematologic picture became more characteristic of acute or chronic lymphocytic leukemia during the course of the disease. These cases were included in this study and considered to be clinical transformations to leukemia from the original category of lymphosarcoma as a result of bone marrow invasion by the lymphosarcomatous process. This transition can occur in all three histologic groups. The disease is indistinguishable, at the onset, from the remainder of the group, both clinically and histologically.

#### HISTOLOGIC CLASSIFICATION

Pathologists and clinicians have largely come to realize that the histologic appearance does not define with much degree of certainty the clinical course, extent of involvement and prognosis of these diseases. The problem is further complicated by the fact that small cell lymphosarcomas cannot be differentiated from the leukemias of lymphatic origin on the basis of microscopic appearances alone.<sup>3-7</sup>

It is admitted that no completely satisfactory basis for classification of lymphoid tumors has received widespread acceptance. Only the better differentiated pictures of Hodgkin's disease and giant follicle lymphosarcoma can be easily separated from the remainder of the general group of lymphosarcomas. We have therefore continued to use the classification that appears to have the widest acceptance and has been utilized by the Pathology Department of the Memorial Center.<sup>4, 6, 8, 9</sup> The general term, lymphosarcoma, is used to include all primary malignant tumors of lymphoid origin except Hodgkin's disease, and can be divided into three types:

*Giant Follicle Lymphosarcoma (GFLSA)*: This group includes the characteristic picture of giant follicle formation, as well as lymphosarcoma that has largely retained follicular features.<sup>10-11</sup> Transitions of this histologic pattern to the other two groups are often seen, and in borderline cases the separation of this group from the less differentiated forms is largely arbitrary.

*Reticulum Cell Sarcoma (RCSA)*: In this group the predominant cell type is greater than one and a half times the size of the mature lymphocyte, and includes the groups designated by others as retothelsarcoma,<sup>12</sup> reticulum cell lymphosarcoma,<sup>9</sup> clasmatocytic and stem cell lymphomas,<sup>13</sup> lymphoblastoma,<sup>7</sup> anaplastic sarcoma of lymphoid origin,<sup>14</sup> and most of the group designated as lymphoblastic lymphoma.<sup>13</sup>

*Lymphosarcoma (LSA)*: The predominant cell type is similar to the



mature lymphocyte, and includes the groups designated as lymphosarcoma-lymphocytic cell type,<sup>9</sup> lymphocytic lymphoma,<sup>13</sup> lymphocytoma,<sup>7</sup> and some forms of lymphoblastic lymphoma.<sup>13</sup>

For more detailed histologic descriptions of the various groups described above, the original articles should be consulted.

A total of 1,635 patients' records were available for study, selected as outlined above. Of these, 366 were excluded, usually because of the lack of an adequate tissue examination at this institution, or because of lymphocytic leukemia from the first Memorial Center visit. The remaining 1,269 cases comprise the study group. These included 162 cases of giant follicle lymphosarcoma (GFLSA), 554 cases of reticulum cell sarcoma (RCSA), and 553 cases of small cell lymphosarcoma (LSA).

#### AGE AND SEX DISTRIBUTION

The age range, at the time of the probable clinical onset of the disease, extends from 22 months to 92 years. As seen in figure 1, the greatest number of cases occurs during the fifth decade of life, and the median age for the entire group is 49.7 years. The group is approximately 15 years older than a similar group of patients seen at this institution with Hodgkin's disease.<sup>15</sup>

The diseases occur more frequently in males than in females, in all age groups, the average ratio being 1.7 to 1. The male preponderance was greatest in late childhood, reaching a maximum of 4.5 to 1 in the group 11 through 15 years of age. At the extremes of age, this ratio approaches unity, as is graphically demonstrated in figure 2.

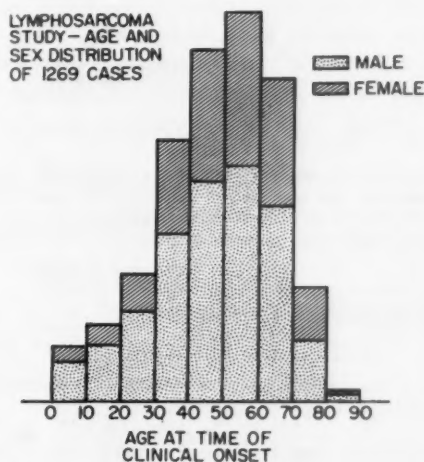


FIG. 1. Age and sex distribution of 1,269 cases of lymphosarcoma.

## LYMPHOSARCOMA RATIO OF MALES TO FEMALES

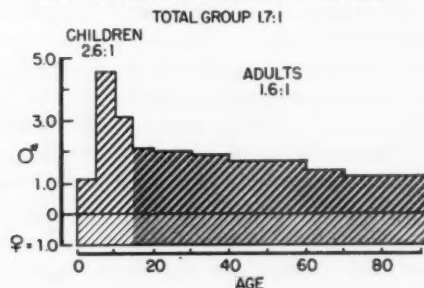


FIG. 2. Lymphosarcoma: ratio of males to females.

## TRANSITIONS TO LEUKEMIA

The difficulty in distinguishing patients with lymphosarcoma from those with lymphocytic leukemia has been discussed, in part, in the presentation of the criteria for selection of cases for this study. It is often impossible to determine on physical examination, or even on histologic study of a lymph node, whether a patient is suffering from lymphosarcoma or a variety of lymphocytic leukemia. Even after study of the peripheral blood and the bone marrow morphology, the distinction between these two groups may not be sharp, and must be made on an arbitrary basis. Yet we feel it is desirable to separate those patients with bone marrow involvement and the picture of leukemia from those without such changes. The generalization of the disease and the compromise of bone marrow function in those patients with leukemic changes demand an approach to therapy quite different from that for patients with relatively localized lymphosarcoma.

Table 1 lists the "leukemic" transitions that were seen in 97 patients, or 7.6% of the total series. It can be seen that these changes occurred

TABLE 1

The Frequency of Acute Leukemia (AL), Chronic Lymphocytic Leukemia (CLL) and Leukolymphosarcoma (LLSA) in 1,269 Patients with Lymphosarcoma Who Presented Initially Without Leukemic Changes

Initial Diagnosis	No. Cases	AL		CLL		LLSA		Total	
		No.	%	No.	%	No.	%	No.	%
GFLSA	162	2	1.2%	5	3.1%	7	4.3%	14	8.6%
LSA	553	6	1.1%	25	4.5%	39	7.0%	70	12.6%
RCSA	554	2	0.4%	4	0.7%	7	1.3%	13	2.4%
Total	1,269	10	0.8%	34	2.7%	53	4.2%	97	7.6%
Children	69	5	7.2%	0	0.0%	4	5.8%	9	13.0%
Adults	1,200	5	0.4%	34	2.8%	49	4.1%	88	7.3%

most commonly in the group with small cell lymphosarcoma (12.6%) and giant follicle lymphosarcoma (8.6%). Only six patients with reticulum cell sarcoma showed complete leukemic transitions, two of these of the acute stem cell type. These abnormalities in the blood and bone marrow were seen more often in children than in adults, and in all of the five children who showed this change the leukemia was of the acute stem cell variety. Although five cases of acute leukemia were observed in adults, the picture is usually that of chronic lymphocytic leukemia.

### RESULTS OF THERAPY

The value of radiation therapy in the treatment of patients with lymphosarcoma is well established.<sup>4, 16-18</sup> The comparative radiosensitivity of these

#### LYMPHOSARCOMA STUDY -- ANALYSIS OF TREATMENT

##### RADIATION THERAPY

###### FIRST COURSE (1102)

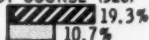


###### SECOND COURSE (766)



##### ALKYLATING AGENTS

###### FIRST COURSE (326)



###### SECOND COURSE (157)



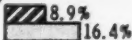
##### "ANTI-METABOLIC DRUGS"

(41)



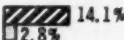
##### ADRENAL STEROIDS and/or ACTH

(158)



##### RADIOACTIVE PHOSPHORUS

(71)



OBJECTIVE BENEFIT "Complete" Partial\*

SUBJECTIVE BENEFIT, ONLY

Partial response -- objective decrease in size of tumor, sustained for a minimum of one week, without spread of disease elsewhere

"Complete" response--absence of all palpable or visible evidence for a minimum of one month.

FIG. 3. Analysis of treatment in lymphosarcoma.

tumors generally permits some degree of symptomatic improvement, but it is not known whether this treatment has significantly prolonged survival.

Many other agents have been used, and some have received enthusiastic support. At intervals, interest has been renewed in the possibility of surgical cure in certain localized forms of lymphosarcoma.<sup>6, 17, 19, 20</sup>

It is difficult to compare the results of different forms of treatment in a chronic disease which has a highly variable natural history and for which there is no cure. No studies have been reported, nor is the present review an example, of a randomized, well controlled, concurrently running analysis and comparison of different therapeutic regimens. However, an attempt has been made to study the therapeutic results observed during the 30-year period of this review.

Figure 3 shows the results obtained with the five agents used most frequently during the period of this study. By "complete" response is meant complete freedom from grossly detectable disease for a period of at least one month after the completion of or while receiving therapy. All other instances of objective regression, lasting for a period of at least one week, without concomitant spread of disease elsewhere, were classified as "partially" benefited. If systemic therapy was given with radiation therapy, benefit was not attributed to the drug unless areas of disease not treated with radiation showed improvement.

#### RADIATION THERAPY

The first course of radiation therapy resulted in objective improvement in 78.4% of the 1,102 patients treated; in over 20% the benefit was classified as complete. The second course of therapy gave almost equal results. In general, the degree of response noted during the first course of radiation therapy was observed after the second. In most cases, the usefulness of radiation therapy was eventually limited by the generalized spread of the disease, by increased radioresistance of the tumor, and by diminished tolerance of the patient.

#### ALKYLATING AGENTS

Since the early 1940's, nitrogen mustard and related drugs have been extensively employed in patients with tumors of lymphoid origin.<sup>21-23</sup> Though several experimental agents were used in this series of patients, the majority of patients received either HN-2 (methyl-bis[beta-chloroethyl]-amine) or TEM (triethylene melamine).

Objective benefit, not attributable to simultaneously administered radiation, was observed in 19.3% of patients after the first course of treatment, and in 10.8% after the second. In only two instances did this improvement meet the criteria of complete benefit.

## ANTIMETABOLIC DRUGS

A total of 41 patients of this group received various folic acid or purine antagonists. Objective benefit, partial only, was recorded in 29.3%. Ten of this group of patients had had leukemic changes before the use of anti-metabolic drugs. Seven of the 10 did not respond; the remaining three had a partial improvement.

## ADRENAL STEROIDS AND ACTH

Soon after it became known that stimulation of the adrenal gland or the administration of adrenal steroids had an effect on lymphatic tissue, these agents were used in the treatment of lymphosarcoma, with reported benefit in some patients.<sup>24</sup> In addition to their effects on the tumor, these agents may achieve symptomatic improvement by temporarily suppressing pain and fever, and by restoring in some measure lost weight, strength and sense of well-being.

One hundred fifty-eight patients have received this type of therapy, the majority since 1950. Many of these patients had advanced disease, and had received several courses of radiation therapy and antitumor chemotherapy. Though further chemotherapy in such cases was often contraindicated by hematopoietic depression, some form of treatment was demanded by continuing or recurrent constitutional symptoms. Adrenal steroids and ACTH were used most often in such patients in an attempt to improve the quality of their survival. In 8.9% of these patients, partial benefit resulted. This benefit was objective, but usually brief, rarely lasting more than several weeks.

The patient with lymphosarcoma who develops a frank hemolytic anemia may be materially benefited by the use of adrenal steroids and ACTH, and sometimes temporary improvement is seen in the hemorrhagic manifestations of patients with profound thrombocytopenia.

## RADIOACTIVE PHOSPHORUS

Radioactive phosphorus in the treatment of lymphosarcoma initially received enthusiastic support, but is now generally restricted to those patients showing the transition to chronic lymphocytic leukemia.<sup>25-28</sup> Seventy-one patients with lymphosarcoma were treated with radioactive phosphorus during the period of this study, 14.1% showing objective improvement.

## COMBINATION THERAPY

In certain situations the intravenous administration of a rapidly acting alkylating agent immediately prior to radiation therapy is indicated. These are instances where radiation therapy alone can aggravate the precarious state of patients with tumor compression of the superior vena cava, trachea

TABLE 2  
Types of Radical Surgical Procedures in 76 Patients with Lymphosarcoma.

Procedure	GFLSA	RCSA	LSA	Total
Neck dissection	2	11	6	19
Axillary dissection	1	5	1	7
Groin dissection		1	1	2
Supraclavicular dissection		1		1
Gastrectomy		12	9	21
Bowel and nodes		3	2	5
Abdominal-perineal resection		1		1
Pelvic exenteration			1	1
Head and neck procedure		4	2	6
Extremity amputation		11		11
Wide skin excision	1	1		2
Total	4	50	22	76

or spinal cord. The alkylating agent seems to allow the use of larger and more frequent increments of radiation.<sup>18</sup>

#### RADICAL SURGERY

We have evaluated the results of surgical attempts to eradicate lymphosarcoma. Such an evaluation should be interpreted with the realization that this is a retrospective study. These groups were not randomly selected, and undoubtedly are entirely comparable. Surgical procedures were usually attempted for only very early, well localized disease. Seventy-six such procedures were accomplished in this group of patients, and are summarized in table 2.

Table 3 compares the end results and five-year survivals of these patients with those with the same extent of disease treated by nonsurgical methods, predominantly radiation therapy. These data indicate that the nonsurgi-

TABLE 3  
End Results and Survival Data on Patients with Localized Lymphosarcoma,  
Comparing Surgical and Nonsurgical Management

	Stage I		Stage II	
	217		396	
Patients in Group	24%		6%	
% Treated with Surgery				
	Radical Surg.	Other Therapy	Radical Surg.	Other Therapy
Patients in Group	52	165	23	373
End Results (%)				
Total Known Dead	72.1	55.1	78.3	78.5
Total Lost	13.5	15.1	13.0	7.6
Total Known Alive	14.4	29.8	8.7	13.9
Alive, N.E.D.*	13.5	21.2	8.7	5.6
% Five-Year Survivals	28.8	52.2	13.0	23.9

\* No evidence of disease for at least one year.



TABLE 4  
Analysis of 19 Patients Who Underwent Radical Neck Dissections for  
Localized Lymphosarcoma

Case No.	Age	Sex	DX.	Stage	X-Ray	Recurrence (Mos.)	Duration (Mos.)	End Result
0734	41	M	RCSA	II	No	Unknown	1*	Dead of dis.
1045	11	M	RCSA	II	No	1	4	Dead of dis.
1073	3	F	LSA	I	No	1	4	Dead of dis.
0329	49	M	LSA	II	No	2	5	Dead of dis.
1152	60	M	RCSA	I	No	1	7	Dead of dis.
1146	13	M	LSA	II	Yes	2	10	Dead of dis.
1164	50	M	RCSA	I	Yes	8	13	Dead of dis.
0668	11	M	RCSA	II	No	4	16	Dead of dis.
1166	52	M	RCSA	I	No	9	16	Dead of dis.
0614	34	M	RCSA	I	No	10	17	Dead of dis.
0659	51	F	RCSA	I	No	21	28	Dead of dis.
1153	50	F	LSA	I	No	Unknown	38	Dead, ? cause
0932	58	F	GFLSA	O	No	24	80	NED†
1107	69	M	LSA	I	No	11	88	Dead of dis.
1239	54	M	RCSA	II	No	None	93	NED†
1115	19	M	LSA	II	Yes	7	94	Lost, NED†
0951	39	M	GFLSA	I	No	None	168	NED†
1109	11	F	RCSA	I	Yes	17‡	203	NED†
1116	40	M	RCSA	I	Yes	6	291	NED†

\* Operative morbidity and mortality, with hemorrhage, nerve injury and pneumothorax.

† No evidence of disease for at least one year.

‡ Second partial radical neck dissection on opposite side for recurrent disease, with post-operative x-ray therapy.

cally treated group with stage I disease did significantly better than did those treated with surgery. The data are less conclusive in the groups with stage II disease, though the tendency is again in favor of the nonsurgically treated patients.

The entire story, however, is not told from the over-all survival figures. Table 4 lists the 19 patients who underwent radical neck dissections. Six patients of this group have survived for long periods without evidence of disease. Three of these patients received radiation therapy to the surgically treated area postoperatively. Of the group of six patients, in four the disease recurred in other sites from seven to 24 months after surgery. In three cases, radiation therapy has controlled the disease for periods of from five to 25 years. The fourth patient underwent a partial radical neck dissection on the opposite side as well, with postoperative radiation, and is now well, more than 15 years later.

TABLE 5  
Complications of Therapy for Lymphosarcoma

	No. of Cases	Per Cent
Radiation therapy	1,102	1.9
Alkylating agents	326	3.1
Antimetabolic drugs	41	4.9
Steroids and/or ACTH	168	10.0
Radical surgery	76	13.1
Radioactive phosphorus	71	15.5

It is concluded from this analysis that radiation therapy remains the treatment of choice in this group of diseases because of the high degree of radiosensitivity of these tumors and the frequency of multicentric foci of lymphosarcoma in cases with apparently well localized disease.

#### COMPLICATIONS OF THERAPY

In the final evaluation of any therapy, the frequency of serious complications must be compared to the expected frequency of benefit.

Of the 1,102 patients who received radiation therapy, 21, or 1.9%, developed severe complications. These were radiation osteitis, persistent and severe radiation pneumonitis and fibrosis, severe skin ulcerations requiring plastic surgical repairs, severe iritis and glaucoma, and aggravation of tracheal and superior vena cava obstruction.

The use of alkylating agents resulted in irreversible bone marrow damage in 3.1% of those who received these drugs. In addition, two patients who received nitrogen mustard developed severe uric acid nephropathy, one of these being fatal.

Bone marrow aplasia was encountered in one patient, or 2.4% of the group who received antimetabolic drugs. Another patient, who was given four courses of 6-mercaptopurine, developed jaundice with each course of treatment, and at post mortem had extensive postnecrotic cirrhosis without tumor.

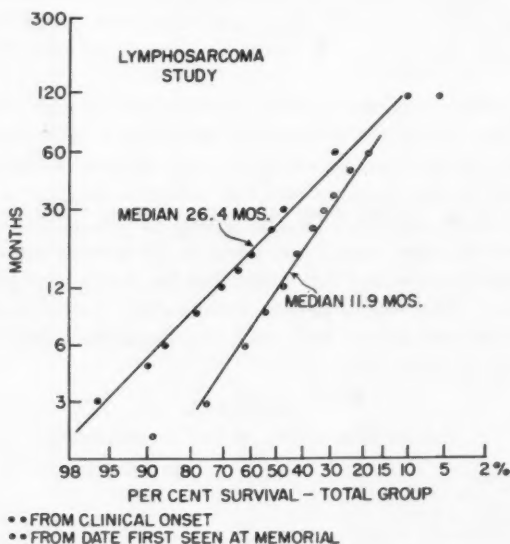


FIG. 4. Survival curves of 1,269 patients with lymphosarcoma (plotted on log-probability paper).

TABLE 6  
Survival Data of 1,269 Patients with Lymphosarcoma

Group	No.	From Clinical Onset			From First Memorial Visit		
		Two years	Five years	Median* (mos.)	Two years	Five years	Median* (mos.)
Total	1,269	52.5%	28.4%	26.4	35.2%	18.5%	11.9
Age:							
0-15	69	23.2	17.4	7.5	17.4	13.0	3.9?
16-92	1,200	54.2	29.0	27.7	36.3	18.8	12.6
Sex:							
Male	790	50.4	26.5	24.2	34.4	17.3	10.5
Female	479	57.1	32.2	32.8	36.5	20.4	13.2
DX:							
GFLSA	162	85.2	55.4	72.0	64.8	33.9	48.0
LSA	553	51.3	27.0	25.2	35.8	18.6	11.7
RCSA	554	44.1	22.6	21.4	26.0	13.9	8.2
Stage:							
O-I	245	66.3	46.6	51.0	55.7	40.7	34.5
II	397	44.9	23.2	22.2	30.8	17.7	10.5
III	627	52.0	24.5	25.5	30.0	10.4	8.4
Year:							
1928-34	95	53.1	29.2	26.8	34.8	17.9	12.8
1935-39	122	57.8	34.7	28.7	42.7	26.2	18.1
1940-44	274	53.3	29.6	27.8	36.2	22.6	13.2
1945-49	385	47.6	26.0	22.6	34.6	19.5	10.6
1950-52	309	51.8	25.9	26.6	36.8	15.5	11.4

\* Medians from curves of all data plotted on log-probability paper.

ACTH or adrenal steroids were given to 158 patients. A total of 16, or 10.1%, developed complications thought to be directly related to this therapy. There were gastrointestinal ulcerations, usually unsuspected, overwhelming monilia or bacterial infections, moderate to severe psychoses, severe osteoporosis with fractures, and aggravation of diabetes and congestive heart failure. These complications occurred despite the use of available preventive measures.

Ten, or 13.1%, of the 76 patients who underwent radical surgery developed severe postoperative complications. In eight of these instances these complications appeared to be the direct cause of death.

Of the 71 patients who received radioactive phosphorus, 11 or 15.5%, developed irreversible bone marrow depression or aplasia.

#### PROGNOSIS AND SURVIVAL

To evaluate the survival curves and to determine what differences, if any, can be shown to exist between various subgroups, the percentage of surviving patients has been plotted on log-probability paper, as shown in

figure 4. The data have been plotted as percentage of survival after the clinical onset of disease, as well as duration from the first Memorial visit. Plotted in this way, these data are linear over a wide range about the median, and allow a better estimate of the median duration of disease than would be available from the crude data. The level of significance of difference between two curves can be determined by applying the "t" test to differences in median survival, as determined from the most objective data—that is, from the duration of life after the first Memorial visit.<sup>29, 30</sup>

Table 6 shows the survival data for the various subgroups studied. All information was taken from survival curves as described above. The data from the clinical onset of disease shed some light on the natural history of lymphosarcoma in various settings. The data from the first Memorial visit are more accurate for statistical purposes and are comparable, one group to another. Yet they do not describe the course of the disease, as the onset always antedated the first hospitalization, and the diagnosis in most cases was made prior to this date.

Certain observations concerning survival can be emphasized by the survival curves, as presented in figures 5 through 10.

The disease in children is more rapidly fatal than in adults. Though 17.4% of the children do survive five years or more, when the disease takes a downhill course it does so at an accelerated rate.

As is well known, giant follicular lymphosarcoma is a much more benign disease than the other two groups. The group of patients with small cell lymphosarcoma survives slightly but significantly longer than does the group with reticulum cell sarcoma.

It is interesting to note that female patients do somewhat better than male patients, as measured by survival rates. This is true for all age groups, but is not evident for the group with giant follicular lymphosarcoma.

As would be expected, those patients with localized disease at the time of the first Memorial visit survive much longer than the remainder of the groups. However, the difference in survival between clinical stage II and stage III disease is not significant at the 5% level.

We have noticed that patients with an absolute lymphocytopenia, as a group, do quite poorly. If survival is analyzed as a function of the total lymphocyte count, when first seen, a very significant separation of patients can be made, as is shown in figure 9. The prognostic value of the total lymphocyte count is as great as for any other feature of the illness. Often the lymphocytopenia is related to widespread disease, and to extensive prior radiation and chemotherapy.

Since the early 1940's new agents have been introduced for the treatment of lymphoid tumors. The alkylating agents, antimetabolic drugs and adrenal steroid therapy have at one time or another received enthusiastic support. Great advances in blood replacement and the treatment of bac-

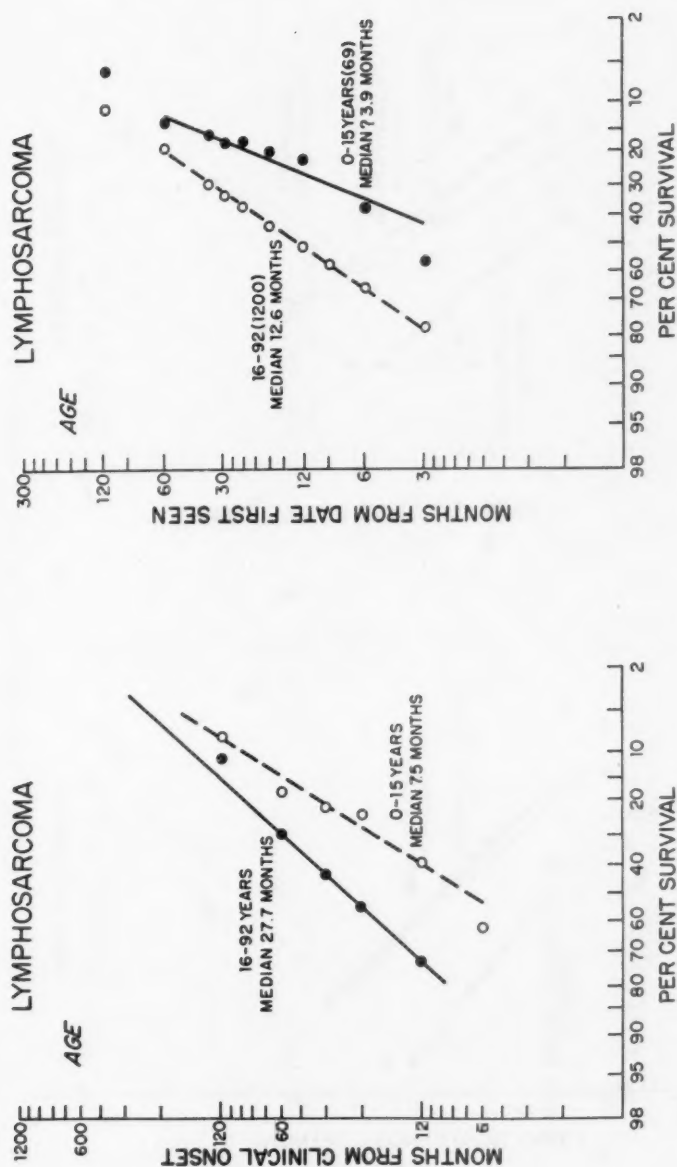


Fig. 5. Lymphosarcoma survival curves: children vs. adults.

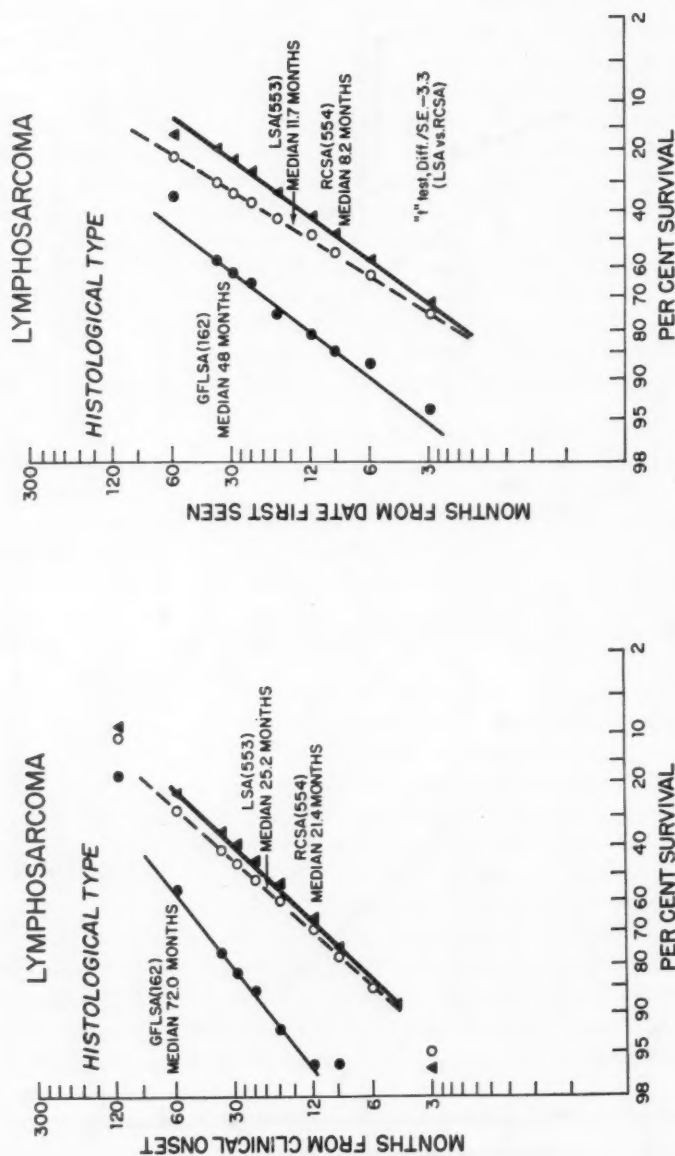


Fig. 6. Lymphosarcoma survival curves: histologic types.



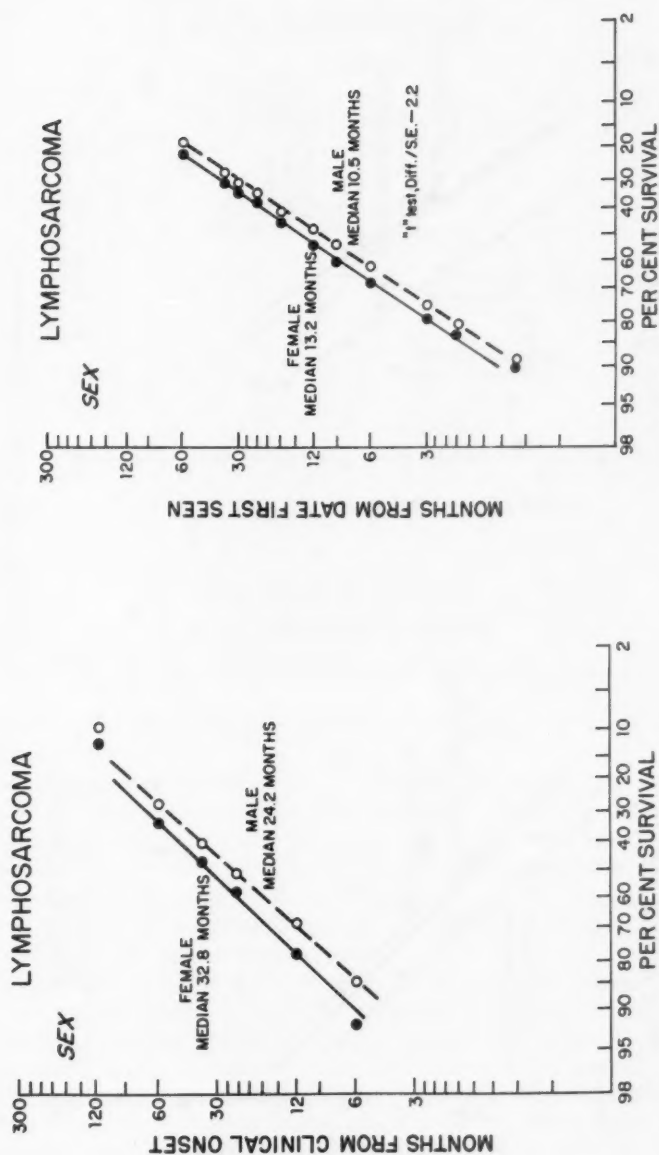


Fig. 7. Lymphosarcoma survival curves: male vs. female.

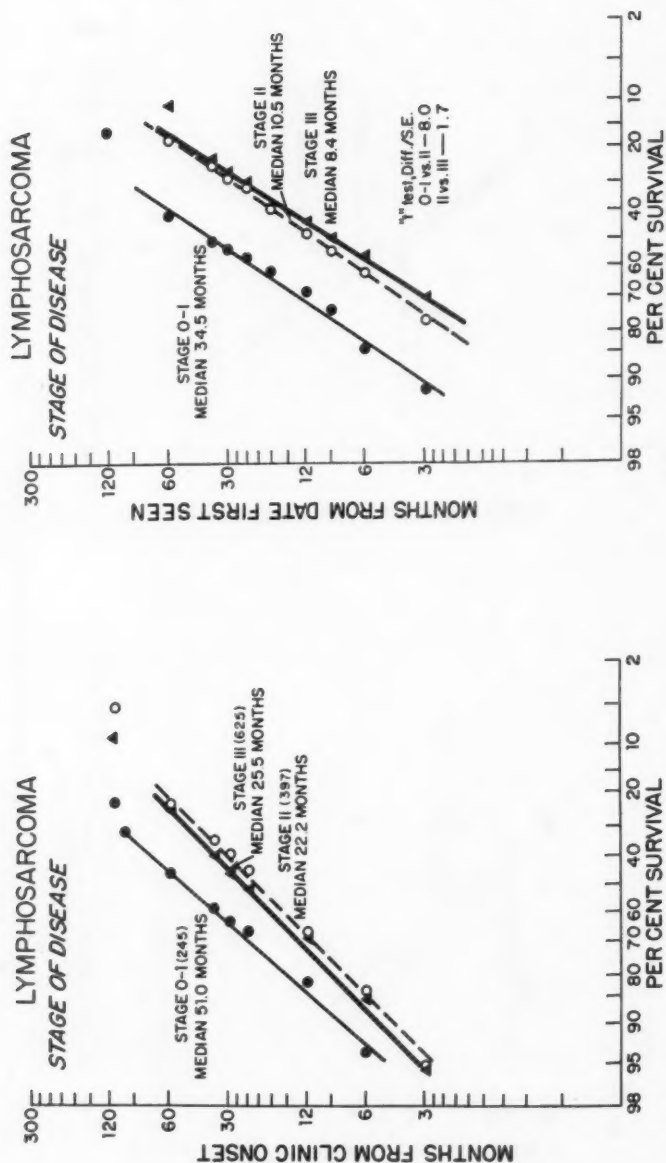


FIG. 8. Lymphosarcoma survival curves: stage of disease on admission.

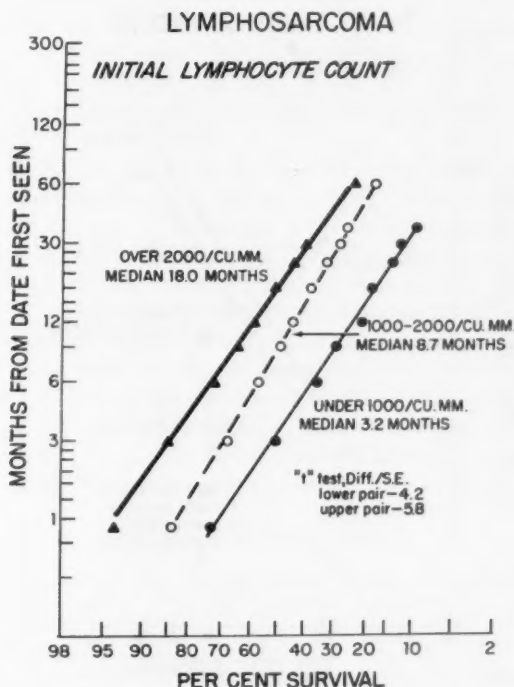


Fig. 9. Lymphosarcoma survival curves: initial total lymphocyte count.

terial infections should have contributed to the longer survival of patients with lymphosarcoma.

Survival curves were analyzed as a function of the year of admission to Memorial. These curves (figure 10) indicate that no improvement in survival has resulted since 1928. Only the period from 1935 to 1939 stands out as showing better results than all periods before and after. Even this improvement is only slight. It is difficult to know if changing diagnostic criteria over the years or an increasing percentage of critically ill patients in recent years has influenced these results.

It is unfortunate that we have no group of nontreated patients to compare with those receiving radiation therapy. However, it would appear that radiation therapy can provide as good results, as measured by survival, as the newer agents introduced since 1940. Gross survival curves do not provide information concerning the quality of survival. We have all seen isolated cases of substantial improvement after the administration of the newer therapeutic agents. Specific problems, such as superior vena cava obstruction and spinal cord compression, undoubtedly respond more quickly and more safely with combination therapy than with radiation alone. There-

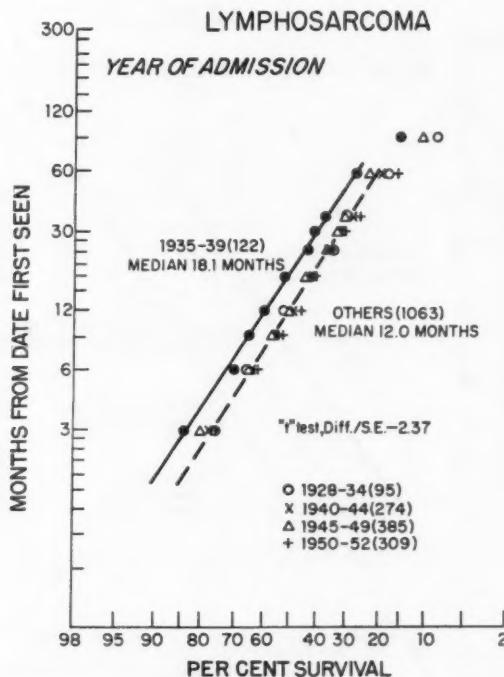


FIG. 10. Lymphosarcoma survival curves: year of admission to Memorial Center.

fore, we are not entirely justified in evaluating the new therapeutic agents on the basis of an analysis of gross survival data alone.

#### SUMMARY

A review has been completed of the experience at Memorial Center for Cancer and Allied Diseases with the group of diseases known generally as lymphosarcoma. All histologically proved cases were studied as of January 1, 1958, if admitted to this institution between 1928 and 1953, thus providing a five-year follow-up period.

Histologic pictures were divided into three groups: giant follicular lymphosarcoma, 162 cases; small cell lymphosarcoma, 554 cases; and reticulum cell sarcoma, 553 cases. Patients with manifest leukemia when first seen at this institution were excluded.

The age and sex distribution indicates a median age for the entire group of 49.7 years, and a ratio of males to females of 1.7 to 1.0.

The frequency of a leukemic transition was noted in 7.6% of the entire group, and is related to the age and histologic classification.

The objective and subjective response to treatment is presented for radiation therapy, 1,102 cases; for alkylating agents, 326 cases; for anti-metabolic drugs, 41 cases; for adrenal steroids and/or ACTH, 158 cases; and for radioactive phosphorus, 71 cases. The frequency of complications of therapy is also presented.

A group of 76 patients undergoing radical surgery is compared to a group with comparable disease receiving nonsurgical treatment.

The over-all five-year survival rate from clinical onset of patients with lymphosarcoma is 28.4%. The median survival from clinical onset is 26.4 months. The survival figures as affected by the histologic group, age, sex, stage of disease, and year of admission are presented. The absolute level of the circulating lymphocytes can serve as a valuable indication of prognosis; the lower the level, the shorter the survival.

It is concluded that radiation therapy remains the treatment of choice for lymphosarcoma, and that no increase in survival can be demonstrated over a period of 25 years, despite the addition of antibiotics, steroids and alkylating agents to the therapeutic program of conventional radiation therapy.

#### SUMMARY IN INTERLINGUA

Esseva completate un revista del experientias al Centro Memorial pro Cancere e Morbos Affin a New York in le tutela de pacientes con morbos del gruppo generalmente designate como lymphosarcoma. Le data terminal del studio es le 1 de januario 1958, e omne le pacientes admittite a iste institution inter 1928 e 1953 esseva includite in tanto que lor casos esseva histologicamente verificate. Assi un quinquenne periodo de observationes de controlo es providite.

Ab le puncto de vista histologic le serie total esseva dividite in tres grupos: 162 casos de lymphosarcoma a folliculos gigante; 554 casos de lymphosarcoma a micre cellulas; e 553 casos de sarcoma a cellulas de reticulo. Patientes con leucemia manifeste al tempore de lor prime apparition a iste institution esseva excludite.

Le distribution per etate e sexo in le gruppo total revela un etate median de 49,7 annos e un proportion masculine a feminin de 1,7 a 1,0.

Le frequentia de transition leucemic es notate in 7,6% del gruppo total. Illo es relationate al grupos de etate e al classification histologic.

Es presentate le responsa objective e subjective al tractamento. Le tractamento includeva irradiation in 1.102 casos, agentes alcoylante in 326, drogas antimetabolic in 41, steroides adrenal e/o ACTH in 158, e phosphoro radioactive in 71. Es etiam presentate le frequentia de complicationes causate per le therapia.

Un gruppo de 76 casos tractate per chirurgia radical es comparate con un gruppo comparabile tractate sin intervention chirurgic.

Le quinquenne superviventia total, a partir le declaration clinic de lymphosarcoma, es 28,4%. Le superviventia median a partir del declaration clinic es 26,4 menses. Le cifras de superviventia es analysate con respecto a gruppo histologic, etate, sexo, stadio del morbo, e anno del admission. Le nivello absolute del lymphocytos circulante pote servir como un importante criterio del prognose. Quanto plus basse iste nivello, tanto plus curte le superviventia.

Es concludite que therapia radiatori remane le tractamento de election pro lymphosarcoma e que nulle augmento del superviventia pote esser demonstrate pro le periodo de 25 annos in despecto del addition de antibioticos, steroides, e agentes alcoylante al programma therapeutic del irradiation conventional.

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**ENZYMES IN ANEMIA: A STUDY OF ABNORMALITIES OF SEVERAL ENZYMES OF CARBOHYDRATE METABOLISM IN THE PLASMA AND ERYTHROCYTES IN PATIENTS WITH ANEMIA, WITH PRELIMINARY OBSERVATIONS OF BONE MARROW ENZYMES \***

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SEVERAL published studies <sup>1, 2, 3, 4</sup> have shown that patients with megaloblastic anemia have markedly elevated serum levels of lactic dehydrogenase. The sera of patients with sickle cell anemia were found to contain only slightly to moderately elevated levels of this enzyme. In most other forms of anemia the serum levels were within normal limits.<sup>2</sup>

The possibility was considered that these elevations of the serum or plasma lactic dehydrogenase in megaloblastic anemia might reflect an abnormality peculiar to the megaloblastic cell series, consisting of an abnormally high content of lactic dehydrogenase and increased activity of the anaerobic glycolytic cycle. This possibility, added to the increased cellularity of the bone marrow and the known rate of increased "turnover" of the intramedullary <sup>5</sup> and peripheral <sup>6</sup> cells, might explain the increased serum or plasma levels of this enzyme.

It appeared to be of interest to extend this study to other enzymes of carbohydrate metabolism, and to measure the activity of these enzymes in the bone marrow as well as in the erythrocytes and plasma of the peripheral blood in a variety of anemias. Initially, technical difficulties prevented successful study of bone marrow enzymes, but recently it has become possible to assay enzyme activity in bone marrow of four patients with blood loss anemia and in one patient with megaloblastic anemia. In other patients with these diseases, and in patients with sickle cell anemia, thalassemia minor, hypoplastic anemia and other types of anemia, enzyme determinations were performed only in plasma and erythrocytes. Seven representative

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enzymes of the anaerobic glycolytic cycle, the citric acid cycle and the hexose-monophosphate shunt were selected for analysis.

#### METHODS AND MATERIAL

The technic used for the preparation of the blood samples has been previously described.<sup>4</sup> A minor change from this technic has been the substitution of 5% disodium-EDTA for the previously employed 10% solution. Hemoglobin concentration in the final hemolysate was determined by the method of Drabkin.<sup>7</sup>

Bone marrow was aspirated from the anterior or posterior iliac crest. As anticoagulant, a 5% disodium-EDTA solution was used (0.15 ml. per 10 ml. of aspirate). The aspirate was centrifuged at 1-4° C. at a speed of 500 r.p.m. (30 × G) for 20 to 30 minutes and the plasma carefully separated and recentrifuged at 30,000 r.p.m. (59,000 × G). The residual buffy layer and packed red cell volume were washed three times, each time with twice the volume of saline. They were then thoroughly resuspended in 0.3% saline and rapidly centrifuged at 6,000 r.p.m. (4,400 × G) for two minutes. This was repeated twice. The buffy layer, still contaminated with red blood cells, was frozen and thawed three times and homogenized in an Erway homogenizer for three minutes. The volume of the homogenate was adjusted to 5 ml. with distilled water, thoroughly mixed, and then centrifuged at 10,000 r.p.m. (7,000 × G) for 15 minutes. In the resulting supernate, protein was determined by the method of Lowry<sup>8</sup> and hemoglobin by the method of Drabkin.<sup>7</sup> Only minimal enzyme activity was detected in the residue.

The enzyme determinations were performed according to standard methods, with minor modifications, as previously reported.<sup>4</sup> The following enzymes were determined: phosphohexoisomerase (PHI), aldolase (Ald.) and lactic dehydrogenase (LD), which are representative enzymes of the anaerobic glycolytic cycle; malic dehydrogenase (MD) and isocitric dehydrogenase (ICD) of the citric acid cycle; glucose-6-phosphate dehydrogenase (G-6-PD) and 6-phosphogluconic dehydrogenase (6-PGD) of the hexosemonophosphate shunt. The enzyme values in the plasma were expressed as  $\mu\text{M}$  of one of the reaction components per milliliter per minute. The intra-erythrocytic enzyme activity was expressed as  $\mu\text{M}$  per gram of hemoglobin. The enzyme content of  $10^6$  erythrocytes was also calculated, as previously described,<sup>4</sup> but because of the greater reproducibility and reliability of the hemoglobin determination, the activity per unit weight of hemoglobin was adopted for expressing enzyme activity in the red cells. In the case of the bone marrow, enzyme activity was expressed per gram of nonhemoglobin protein. Correction was made for the enzyme activity per gram of hemoglobin as measured in the peripheral blood.\*

The normal values for the enzymes were arrived at by determination of these enzymes in plasma and erythrocyte samples from 20 to 32 normal individuals, as previously reported.<sup>4</sup> The value for ICD in the erythrocytes, previously stated to be  $0.016 (\pm 0.01) \mu\text{M}$  of TPNH per  $10^6$  erythrocytes per minute and  $0.5 (\pm 0.2) \mu\text{M}$  per gram of hemoglobin per minute, has been found to be incorrect on further study. The corrected values are:  $0.042 (\pm 0.015)$ , and  $1.5 (\pm 0.5)$ , respectively.

#### RESULTS

*Megaloblastic Anemia:* The enzyme pattern in the plasma and erythrocytes in this disease is shown in figures 1 and 2. A detailed description of

\* This correction is based on the assumption that the enzyme content of the mature erythrocyte in the bone marrow and in the peripheral blood is the same. This assumption found support in the observation that the first bone marrow washings following osmohemolysis had the same activity as leukocyte-free and platelet-free hemolysates of the peripheral blood.

Plasma Enzymes in Megaloblastic Anemia  
(m $\mu$  M/ml./min.)

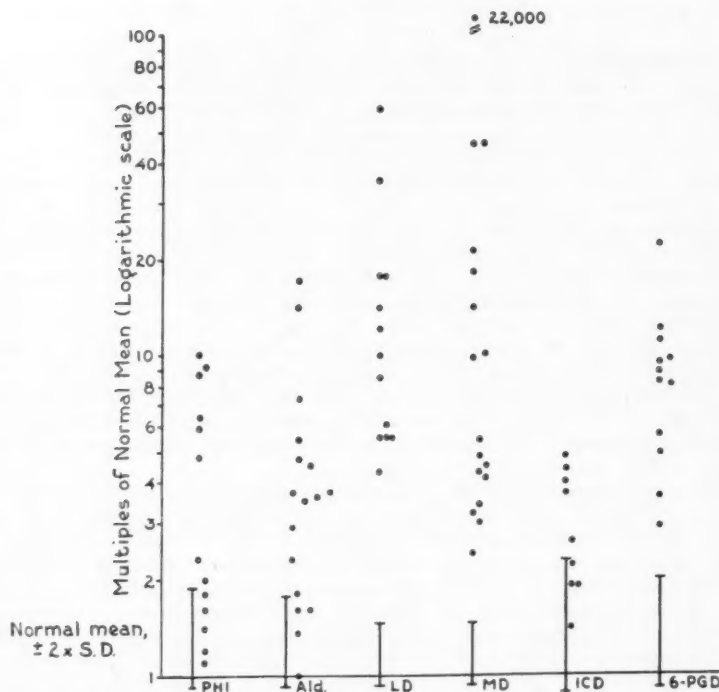


FIG. 1.

these findings has been reported elsewhere.<sup>4</sup> In the plasma (figure 1), LD and MD were found to be most markedly increased, with 6-PGD, Ald., PHI, ICD showing lesser elevations. In the peripheral erythrocytes (figure 2), some of the enzyme values were slightly increased. If the results were expressed in terms of erythrocytes rather than hemoglobin, the abnormalities were somewhat greater because of the macrocytosis.

In one additional patient, with folic acid deficiency associated with chronic alcoholism and mild cirrhosis of the liver, enzyme determinations were performed in the cells (figure 3) and plasma (figure 4) of the bone marrow, as well as in the plasma and erythrocytes of the peripheral blood. This severely malnourished patient had marked megaloblastic hyperplasia of the bone marrow, but the hemoglobin concentration following admission to the hospital was only moderately reduced (to 10 gm.%; the hematocrit to 29%). The reticulocyte count was 1.8%. He had normal absorption of Co<sup>58</sup>-cyanocobalamine, and the urinary excretion of formiminoglutamic acid

### Erythrocyte Enzymes in Megaloblastic Anemia ( $\mu\text{M}/\text{g. Hb.}/\text{min.}$ )

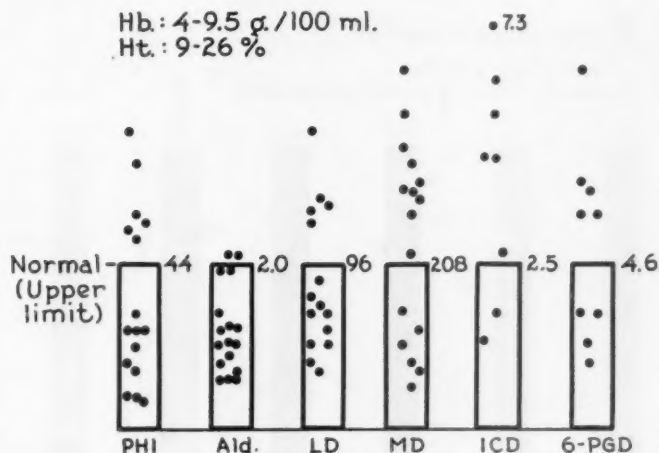


FIG. 2.

### Bone Marrow Enzymes in Megaloblastic and Blood Loss Anemia ( $\mu\text{M}/\text{min.}/\text{g. of non-Hb. protein}$ )

■ Megaloblastic anemia:  
 Hb.: 8 g./100 ml.  
 Serum Fe: 288  $\gamma\%$

▨ Blood loss anemia:  
 Hb.: 5 g./100 ml.  
 Serum Fe: 15  $\gamma\%$

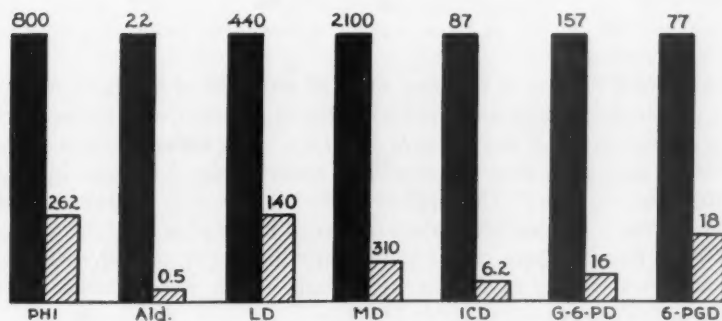


FIG. 3.

Enzymes of Bone Marrow Plasma and Peripheral Plasma in  
Megaloblastic and Blood Loss Anemia  
( $\mu\text{M}/\text{ml}/\text{min.}$ )

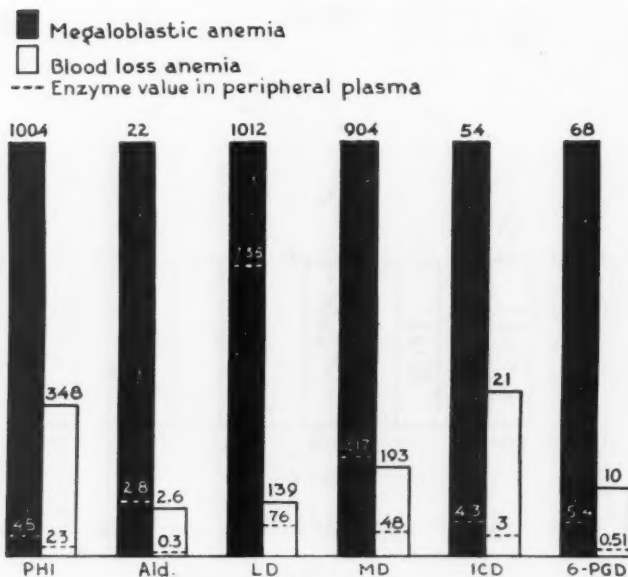


FIG. 4.

following histidine loading<sup>9</sup> was 20,000  $\mu\text{M.}$  in 48 hours. (The normal value in our laboratory<sup>10</sup> is less than 80  $\mu\text{M.}$  in 48 hours.) The enzyme determinations in the plasma were done at intervals following the start of therapy (figure 5). Following the absorption test with  $\text{Co}^{58}$ -cyanocobalamin (which includes the intramuscular administration of 1,000  $\mu\text{g}$  of vitamin  $\text{B}_{12}$ ), an increase in the plasma level of LD and MD was observed, but following the daily parenteral administration of 30 mg. of folic acid there was a rapid decline of these enzyme values, even before the maximal reticulocyte response.

The enzyme content of the bone marrow cells and of the bone marrow plasma in this patient was compared with that of a patient with normoblastic hyperplasia due to blood loss (figures 3 and 4). The enzyme values elicited from the megaloblastic bone marrow were much higher than those obtained from the other marrow. This applied to the marrow cells as well as to the marrow plasma. The enzyme values measured in the plasma of this normoblastic bone marrow were of the same magnitude as those found in three other marrows with normoblastic hyperplasia which were studied during the time of this investigation (table 1).



### Serial Plasma LD and MD Determinations in a Patient with Folic Acid Deficiency

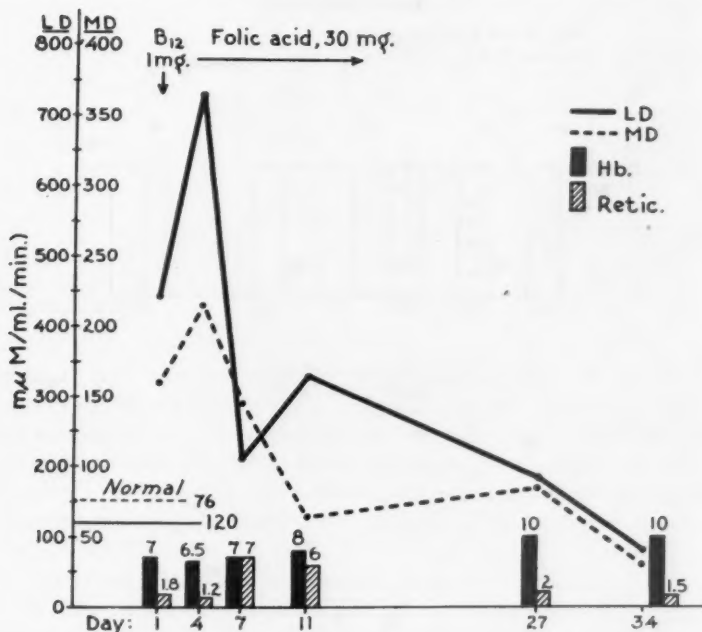


FIG. 5.

*Blood Loss Anemia* (figure 6): The seven patients in this group had chronic recurrent gastrointestinal hemorrhage. Two had duodenal ulcer, and five had recurrent gastrointestinal bleeding associated with chronic alcoholism and mild hepatic cirrhosis. One patient had, in addition, blood

TABLE 1  
Enzyme Levels of Bone Marrow Plasma and Blood Plasma in Blood Loss Anemia\*  
(N: 4)

	Bone Marrow Plasma		Blood Plasma	
	Mean	Range	Mean	Range
PHI	485	255-688	38.5	14-72
Ald	5.1	2.2-11	1.6	0.3-2.7
LD	180	139-217	99	73-125
MD	290	135-603	72	48-108
ICD	34.2	11-80	6.1	3.0-9.1
G-6-PD	18.6	7.2-29	2.1	1.6-2.8
6-PGD	12.3	2.2-26	1.5	0.5-3.2

\* mμM./ml./min.

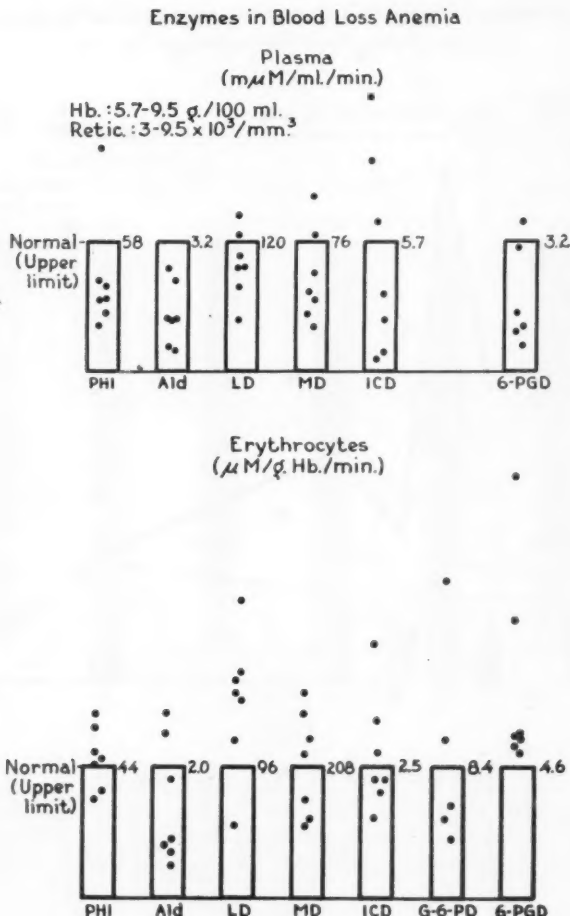


FIG. 6.

loss from a severe laceration of the scalp. None had ascites, jaundice or demonstrable varices. The hemoglobin values ranged from 5.4 to 7.8 gm.%, and the reticulocyte count from  $3 \times 10^3$  to  $9.5 \times 10^3/\text{mm}^3$ . Most of the plasma values were within normal limits, with a few elevations, especially of the isocitric dehydrogenase (figure 6). Of the intra-erythrocytic enzymes, the level of lactic dehydrogenase was abnormal in six of the seven cases. The level of 6-PGD was abnormal in all cases. The Ald. concentration was slightly abnormal in only two patients (figure 6).

The enzyme concentration of the bone marrow extract and bone marrow plasma was lower in the normoblastic than in the megaloblastic bone marrow

TABLE 2  
Plasma Enzymes in Hemoglobinopathies\*  
(17 Patients)

	Normal	Sickle Cell Anemia (N:15)				S-C-Dis. (N:1)	C-C-Dis. (N:1)
		Range	Mean	Median	p Value		
Hb. (gm. %)	13.5-15	4.9-11.1	8.1	8.0	—	7.5	9.6
Retic. $\times 10^3/\text{mm}^3$	50	62-750	345	296	—	150	212
PHI	30( $\pm 14$ )	18-229	61( $\pm 52$ )	40	.05	132	14
Ald	1.8( $\pm 0.7$ )	1.0-7.3	2.7( $\pm 1.5$ )	2.5	<.05	1.7	1.2
LD	82( $\pm 19$ )	169-385	270( $\pm 66$ )	298	<.001	298	101
MD	52( $\pm 12$ )	87-337	200( $\pm 86$ )	193	<.001	106	52
ICD	2.5( $\pm 1.6$ )	1.5-13.0	5.2( $\pm 2.8$ )	4.8	<.01	9.0	2.1
6-PGD	1.6( $\pm 0.8$ )	1.0-14	4.8( $\pm 3.8$ )	3.9	<.01	1.6	1.9

\*  $\mu\text{M.}/\text{ml.}/\text{min.}$

(figures 3, 4). Nevertheless, the bone marrow plasma values for all enzymes were higher than for the peripheral plasma (table 1). This difference was highest for the isomerase and lowest for the lactic dehydrogenase.

*Hemoglobinopathies* (tables 2 and 3): Among the patients of this group there were 15 with sickle cell anemia, one with sickle cell-hemoglobin C disease, and one with homozygous C disease. The pertinent hematologic data are included in tables 3 and 4.

In the plasma, the maximal enzyme elevations were more than three times the upper limit of normal for the LD, and four times the upper limit of normal for the MD. The levels of these two enzymes were elevated in all cases. While there were many normal values for the other enzymes, especially for PHI, Ald., and ICD, the mean value of all enzyme levels was higher than normal (table 2). In the patient with sickle cell-hemoglobin C

TABLE 3  
Erythrocyte Enzymes in Hemoglobinopathies\*  
(16 Patients)

	Normal	Sickle Cell Anemia (N:14)				S-C-Dis. (N:1)	C-C-Dis. (N:1)
		Range	Mean	Median	p Value		
Hb. (gm. %)	13.5-15	4.9-11.1	8.1	8.0	—	7.5	9.5
Retic. $\times 10^3/\text{mm}^3$	50	62-750	345	296	—	150	212
PHI	30( $\pm 7.0$ )	29-95	48( $\pm 20$ )	49	<.01	35	56
Ald	1.2( $\pm 0.4$ )	0.9-3.9	2.2( $\pm 0.8$ )	2.0	<.001	1.7	1.9
LD	60( $\pm 18$ )	83-388	180( $\pm 93$ )	166	<.001	171	177
MD	160( $\pm 24$ )	80-460	245( $\pm 93$ )	230	<.01	305	280
ICD	1.5( $\pm 0.5$ )	0.45-7.5	2.8( $\pm 2.7$ )	2.1	<.2	7.5	1.7
G-6-PD	5.6( $\pm 1.4$ )	2.6-18.0	11.0( $\pm 5.6$ )	10.5	<.01	10.5	
6-PGD	3.0( $\pm 0.8$ )	1.5-9.8	5.4( $\pm 2.1$ )	6.1	<.001	3.2	13

\*  $\mu\text{M.}/\text{gm. Hb.}/\text{min.}$

TABLE 4  
Hematologic Data of Three Patients with Thalassemia Minor

Case	Hb. (gm. %)	Ht. (%)	RBC $\times 10^9/\text{mm.}^3$	Retic. $\times 10^9/\text{mm.}^3$	A <sub>2</sub> Hb. (%)*	Half-life (Cr <sup>51</sup> )
1	11.2	36	4.7	18	16.4	—
2	9.5	33	4.3	120	14.2	31 days
3	9.7	34	3.9	78	24.6	21.5 days

\* Measured by agar gel electrophoresis and automatic scanning of stained electrophoretogram. The upper limit of normal with this technic is 10%.<sup>11</sup>

disease, only the Ald. and 6-PGD were normal; on the other hand, all plasma enzymes in the patients with the homozygous C disease were normal.

In none of the patients was the enzyme content of the erythrocyte completely normal (table 3). LD was abnormal in almost all cases. The lowest elevations and the lowest incidence of such elevations occurred with PHI and Ald. In the patient with sickle cell-hemoglobin C disease, LD, MD, ICD and 6-PGD were elevated; the other enzyme levels were normal.

#### Plasma Lactic Dehydrogenase and Hemoglobin Levels

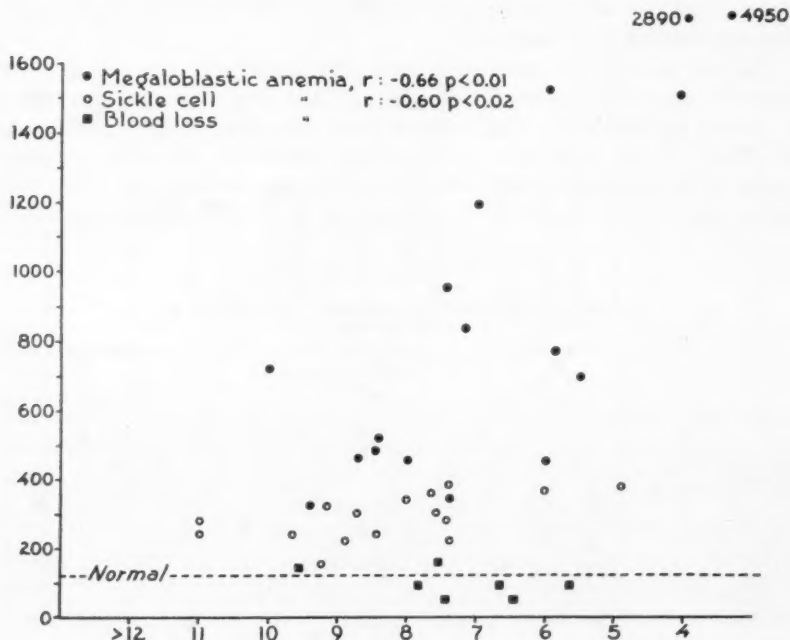


FIG. 7.

In the patient with homozygous C disease, only the Ald. and the ICD levels were within normal limits.

The relationship of the level of the activity of lactic dehydrogenase, which was found to be the most consistently increased enzyme level in the plasma and erythrocytes, to the hemoglobin level and reticulocyte count was statistically explored (figure 7). No statistically significant relationship could be detected between the enzyme level in the plasma or erythrocytes with the reticulocyte count ( $r = +0.45$ ,  $p > 0.1$ ). There also was no statistically significant correlation between intra-erythrocytic LD and the hemoglobin level ( $r = -0.142$ ,  $p > 0.1$ ). There was, however, a significant negative correlation between the hemoglobin level and the plasma level of LD ( $r = -0.60$ ,  $p < 0.02$ ) (figure 7). The correlation was not so marked as in the case of megaloblastic anemia ( $r = -0.66$ ,  $p < 0.01$ ) (figure 7).

*Thalassemia Minor:* Only three patients of this group were available for study. They were adults with minimal symptoms. The physical examination was negative except for mild splenomegaly. The hematologic

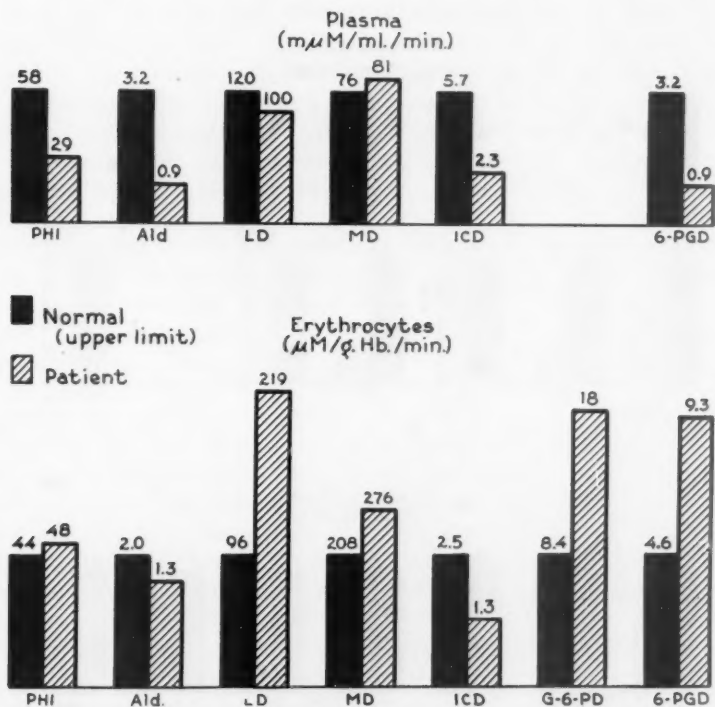


FIG. 8.

data during the time of the enzyme analysis are listed in table 4. All had the characteristic microcytic, hypochromic anemia with many target cells. The mean half-life of the peripheral erythrocytes as measured with  $\text{Cr}^{51}$ -tagged erythrocytes was 31 days in one patient and 21.5 days in the other. This measurement was not made in the third patient.

The mean enzyme values of the peripheral plasma were within normal limits (figure 8), except for one patient (case 1, table 4), who had a slightly elevated MD, and another (case 3, table 4) with a slightly elevated LD level. The intraerythrocytic content of all enzymes, except for the Ald. and ICD, was abnormally high when expressed per gram of hemoglobin. The enzyme content when calculated per  $10^6$  of erythrocytes was less abnormal because of the hypochromia and microcytosis.

*Miscellaneous Anemias:* Only one of the three patients with hypoplastic anemia apparently had no complicating hemolytic process. The plasma levels of the enzymes in this patient were normal except for the ICD and 6-PGD (figure 9). The concentration of all intra-erythrocytic enzymes was within normal limits but low, especially in the case of MD and ICD.

#### Enzymes in Hypoplastic Anemia

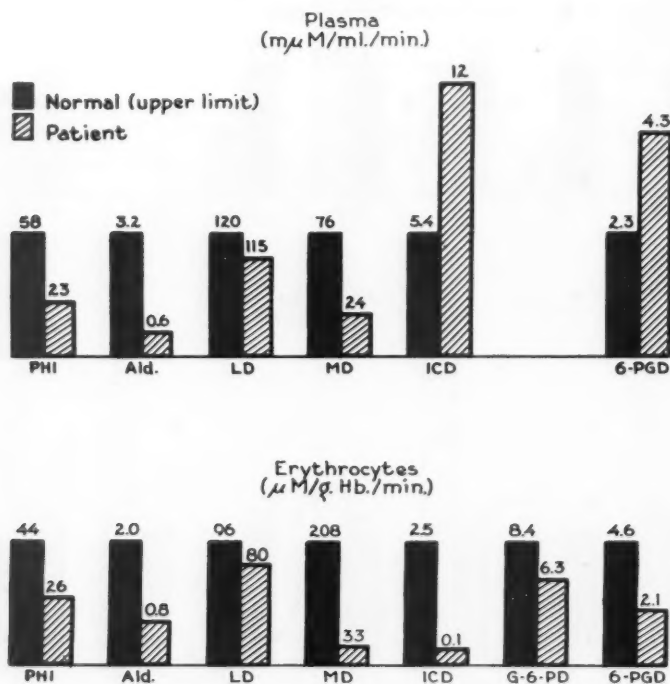


FIG. 9.



The clinical features of patients with other anemias were so complex as to preclude relating plasma enzyme abnormalities, when present, to the hematologic disease *per se*.

The intra-erythrocytic enzyme levels probably depended more directly on the hematologic abnormality. In the four patients with myeloid metaplasia, the intra-erythrocytic levels of LD, MD, G-6-PD and 6-PGD were increased, while ICD levels were increased in only two, and PHI and Ald. in one patient. In the two patients with hyperferricemic hypochromic anemia, the cause of which remained unknown, only the intra-erythrocytic level of LD was increased, and the elevations were slight. In seven patients with anemia secondary to lymphoma, hepatic disease, carcinoma or renal disease, the erythrocyte enzyme levels were found to be irregularly and only mildly elevated.

#### DISCUSSION

The working hypothesis<sup>4</sup> that the high plasma levels of LD and of the other enzymes of carbohydrate metabolism which were determined originate in the bone marrow appears to be supported by the results of the present investigation, although further studies of megaloblastic bone marrows are required for confirmation. The enzyme content of the cellular extract and the plasma from the megaloblastic bone marrow was higher than from the one with normoblastic hyperplasia. This suggests an increased enzyme concentration in the megaloblastic cells, and an increased release of enzymes into the immediately surrounding plasma. This release of enzymes could be accomplished by a high intramedullary destruction rate of megaloblastic cells, which has been considered to be characteristic of the megaloblastic maturation arrest.<sup>5</sup> The increased concentration of marrow enzymes includes not only the enzymes of the anaerobic glycolytic cycle but also enzymes of the citric acid cycle, and enzymes of the hexosemonophosphate shunt. The high enzyme content in the megaloblastic cells may reflect increased metabolic activity or lack of utilization, or both; this problem cannot be satisfactorily settled on the basis of available data. Smith and Baker<sup>12</sup> have recently reported that some of the enzymes which are concerned with pyrimidine synthesis can be found in increased concentration in the peripheral erythrocytes and leukocytes in megaloblastic anemia. These investigators have emphasized the likelihood that this increase is not related to the immaturity of the cells *per se*, but is the result of a "negative feedback" mechanism by which the low concentration of synthesized pyrimidine stimulates the formation of enzymes required in the earlier stages of biosynthesis. It is conceivable that this stimulation also includes the enzymes of the energy metabolism of the cell. Immaturity of the cell, *per se*, does not seem to account for the increase of these enzyme levels, since the enzyme concentration per gram of nonhemoglobin protein is much lower in a normoblastic bone marrow with marked erythroid hyperplasia (figure 3) and

predominance of normal immature cells. In this respect, it is of interest that even the peripheral cells have a slightly increased enzyme content (figure 2). This could represent either increased numbers of "young" erythrocytes in the periphery, or the residue of the marrow abnormality. The reticulocytopenia which characterizes untreated megaloblastic anemia makes the second possibility more likely. Similar conclusions have been reached by Bock and his co-workers<sup>13</sup> on the basis of determinations of the activity of several enzymes of carbohydrate metabolism in peripheral megakaryocytes. The statistically significant negative correlation between the hemoglobin level and the plasma level of enzymes is not surprising, since the anemia itself is a stimulus to bone marrow proliferation, which becomes progressively more abnormal.

The erythroid hyperplasia due to chronic blood loss is characterized by an increase of normal but immature precursor cells. The enzyme content of these cells appears to be lower than those of the megaloblastic cell series (figure 3). This also applies to the bone marrow plasma (figure 4). Nevertheless, the plasma of a bone marrow with normoblastic hyperplasia has been found to have higher enzyme levels than the corresponding plasma of the peripheral blood, where the enzyme levels are normal (table 1). It is of interest that this difference is largest for the enzyme PHI, which is known to be present in high concentration in the short-lived leukocytes.<sup>14, 15</sup> Despite an apparent release of enzymes from the cells of the normoblastic bone marrow into the surrounding plasma, the enzyme concentration in the bone marrow plasma is not sufficient to lead to an increase in the level of the circulating plasma. In the peripheral blood, the enzyme concentration in the red cells is generally increased. This is probably related to the younger cell population. Several investigators have shown that the young erythrocytes and reticulocytes have a higher content of some of the enzymes of carbohydrate metabolism than do older cells.<sup>16, 17, 18</sup>

The hemolytic process in sickle cell anemia occurs predominantly in the intravascular compartment. This appears to be the most likely cause of the enzyme elevation in the plasma.<sup>2</sup> Unfortunately, we have not yet had the opportunity of studying the enzymes in the marrow in this disease. It is of interest that the LD levels in the plasma have been found to be more significantly related to the level of hemoglobin than are the intra-erythrocytic levels of this enzyme (figure 7). It appears that the effect of the intravascular hemolysis upon the plasma levels of this enzyme is greater than the influence of the erythroid hyperplasia and reticulocytosis on the intra-erythrocytic enzyme levels.

The mechanism of the anemia in the thalassemia syndrome is incompletely explored. The variability of the manifestations of this disease has led to the hypothesis of multiple genetic factors as the background of this hereditary disorder.<sup>19</sup> A defect in hemoglobin synthesis, possibly due to deficient incorporation of iron into the erythrocyte protoporphyrin, has been

postulated.<sup>20</sup> The intensity of the hemolytic process, which in this disease also has an extracorporeal component,<sup>21</sup> varies from patient to patient. In one of our patients, hemolysis could not be demonstrated; in the other patient, it was mild. It is of interest that the enzymatic pattern as found in our three adult patients with this disease resembles most the pattern in iron deficiency anemia: the enzymes in the plasma are within normal limits, while the levels of the intra-erythrocytic enzymes are increased. In view of this low degree of demonstrable hemolysis, the possibility must be considered that the enzyme elevations in thalassemia are related less to the high proportion of young cells in peripheral blood than to the genetically determined difficulties in hemoglobin synthesis.

The low levels of intra-erythrocytic enzymes in hypoplastic anemia seem to be best explained by the diminution of the output of young cells from the bone marrow. A complicating factor is perhaps the presence of transfused cells with a diminished survival time. The occasionally associated hemolytic process may contribute to the occasional elevation of plasma enzymes in those patients who require frequent blood transfusions.

As can be seen from the preceding data, the plasma level of lactic and malic dehydrogenase was more consistently abnormal in megaloblastic anemia and sickle cell anemia than were the levels of other enzymes. The basis for this is not known, but it appears that the release of enzymes into the plasma does not depend merely on cell necrosis,<sup>22</sup> but also on other factors, especially proliferative activity of abnormal cells, alteration of surface potentials, anoxia, and the molecular size of the enzyme proteins. Furthermore, after the enzymes are released from tissue, they are subject to inhibition or potentiation, and to different and perhaps specific ways of disposition.<sup>23</sup> Accordingly, the levels of plasma enzymes cannot be precisely equated with the rate of release from tissue.

#### SUMMARY

1. Enzyme abnormalities in the plasma and erythrocytes in various anemias have been described.
2. The mechanism of these abnormalities has been discussed on the basis of enzyme determinations in cellular extracts and plasma of bone marrow from patients with megaloblastic and blood loss anemia.
3. The significance of the plasma levels of enzymes, especially of the LD, for the differential diagnosis of the anemias has been emphasized.

#### ACKNOWLEDGMENTS

The authors wish to thank Mrs. Barbara L. Cunningham and Mr. Clifford D. Fields for helpful technical assistance, and the Medical Illustration Service, Veterans Administration West Side Hospital, for the preparation of the charts.

## SUMMARIO IN INTERLINGUA

Anormalitates del enzymas del plasma e del erythrocytos in varie anemias es describite.

Le marcatamente elevate nivellos plasmatic de dishydrogenase lactic, de dishydrogenase malic, e de dishydrogenase 6-phosphogluconic in anemia megaloblastic in recidiva pare esser relationate al augmentate activitate proliferative del medulla ossee que produce cellulas con un anormalmente alte contento enzymatic e possiblemente etiam al accelerate destruction intramedullari del cellulas precursori megaloblastic, lo que pare esser indicate per le alte nivellos de plasma in le medulla ossee in casos de iste morbo. Augmentate nivellos enzymatic esseva etiam detegite in le erythrocytos peripheric. Le causa possibile de iste phenomeno es discutite.

In anemia a cellulas falciforme, le augmentos del contento plasmatic de enzymas es apparentemente relationate al grado del hemolyse intravasculare e al severitate del anemia. Le nivellos intra-erythrocytic del enzymas depende del distribution del stadios de maturitate del population de erythrocytos. Le cellulas plus juvene ha un plus alte contento de enzymas.

In plure altere anemias, le nivellos plasmatic del enzymas pare depender del grado de hemolyse e del character del associate morbo. Le nivellos intra-erythrocytic pare depender del activitate erythropoietic in le medulla.

Il pare que le alte concentrationes plasmatic de dishydrogenase lactic e malic es characteristic unicamente de anemia megaloblastic in recidiva, sin reguardo al causa. Iste phenomeno se ha provate utile in le diagnose differential del anemias.

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## OWREN'S CAPILLARY BLOOD THROMBOTEST FOR OFFICE OR BEDSIDE CONTROL OF ANTICOAGULANT THERAPY: AN EVALUATION\*†

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THE coagulation proteins in the peripheral blood are in a state of dynamic equilibrium. All of those synthesized in the liver have a life span ranging from a few hours to a maximum of 14 days. The plasma values at any one moment, then, are the resultant of the rate of synthesis and the rate of degradation in both intra- and extravascular locations of these coagulation factors. The indirect anticoagulants act by inhibiting the rate of synthesis in the liver of the following coagulation proteins: prothrombin (II),‡ proconvertin (VII), plasma thromboplastin component (IX), and Stuart factor (X). After the administration of inandione or coumarin derivatives, the proconvertin level falls first, then prothrombin, next (probably) Stuart factor, and finally, plasma thromboplastin component.

The thromboplastin time (Quick)<sup>2</sup> is sensitive to only the proteins involved in the tissue thromboplastin clotting pathway (figure 1). Waaler<sup>3</sup> has shown that the prothrombin and proconvertin (P and P) test system is sensitive to all of these (except proaccelerin and fibrinogen), plus, to a degree, plasma thromboplastin component (PTC) concentration. The theoretic importance of this sensitivity to PTC concentration lies in the ability of such a system to forewarn of acquired hemophilia B-type bleeding secondary to anticoagulant drug-induced PTC deficiency. A test system warning of such impending danger naturally would be of especial importance in anticoagulant drug control.

### RATIONALE OF THE THROMBOTEST

In the Thrombotest, Owren<sup>4,5</sup> has consciously designed a test system that will retain its sensitivity to prothrombin, proconvertin and Stuart factor while accentuating its sensitivity to PTC factor deficiency. This all-in-one reagent, in essence, combines the thromboplastin time and a partial thromboplastin time determination, and becomes increasingly influ-

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‡ Roman numerals in parentheses refer to the designations assigned by the International Committee on Coagulation Factor Nomenclature, Irving Wright, M.D., F.A.C.P., Chairman.<sup>1</sup>

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### A Scheme for Blood Coagulation Fall, 1958

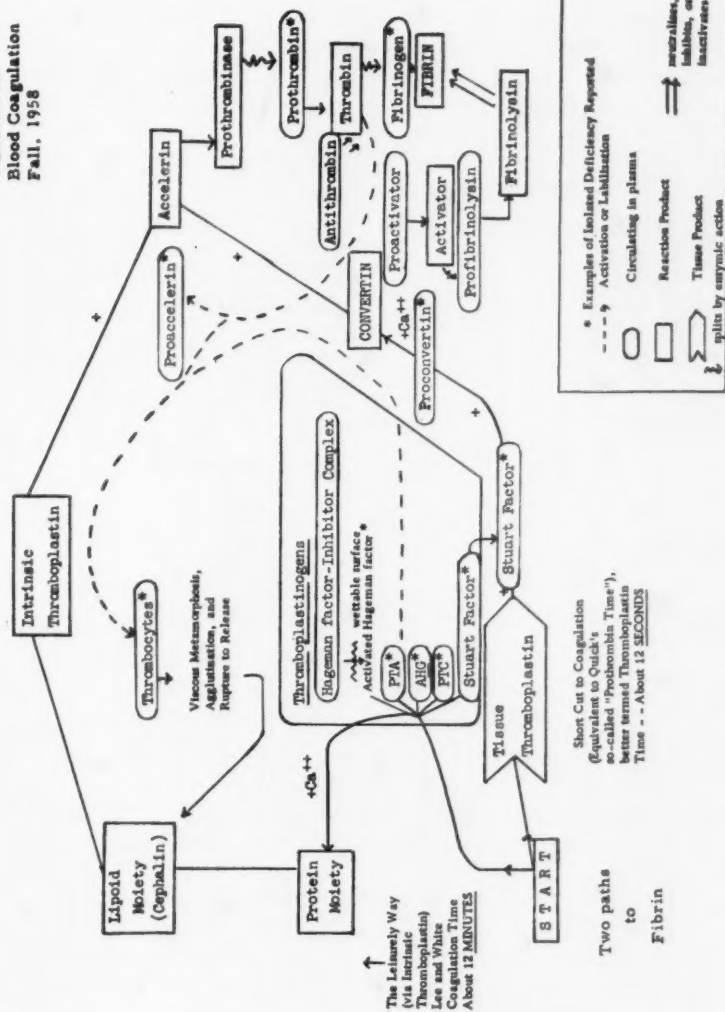


FIG. 1. A scheme for blood coagulation.

enced by PTC and Stuart factor activity as prothrombin and proconvertin values decline. He has selected a tissue thromboplastin derived from a species other than man and giving a slower reaction than human tissue thromboplastin with normal human plasma (40 seconds vs. 12 seconds). He has combined with this a cephalin suspension giving a 50- to 60-second partial thromboplastin time with normal human plasma. Thus as the thromboplastin time lengthens in response to anticoagulant drug therapy, the partial thromboplastin time of the test plasma increasingly influences the vector of activities end point. As in the P and P test system, an

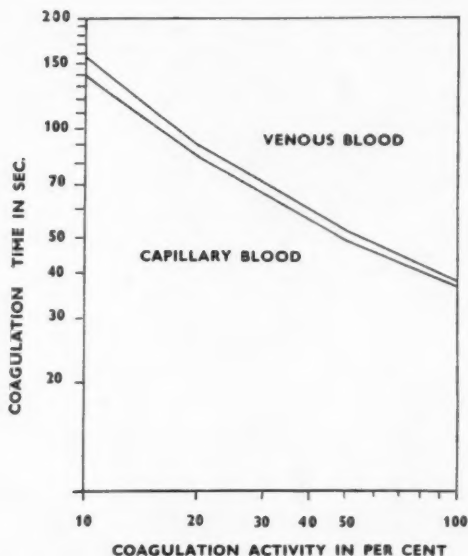


FIG. 2. Control curve as provided with Thrombotest reagent.

adsorbed bovine substrate provides a constant fibrinogen (I) and proaccelerin (V) content for each test. Calcium is added and the combined reagent lyophilized. As such, it is now commercially available.\* For use, it may be reconstituted with the specified amount of distilled water when the test material is capillary blood. Its stability characteristics have been described by Owren.<sup>4,5</sup> In addition, we have found that it may be stored as a frozen liquid at minus 20° C. in 0.5 ml. aliquots, so that a pair of tubes need merely be thawed and warmed to 37° C. upon the arrival of the patient.

The important advantages of the capillary blood method lie in the fact that venipuncture, needle, syringe and centrifuge are by-passed. The test

\* Nyegaard & Co. A/S, Oslo, Norway.

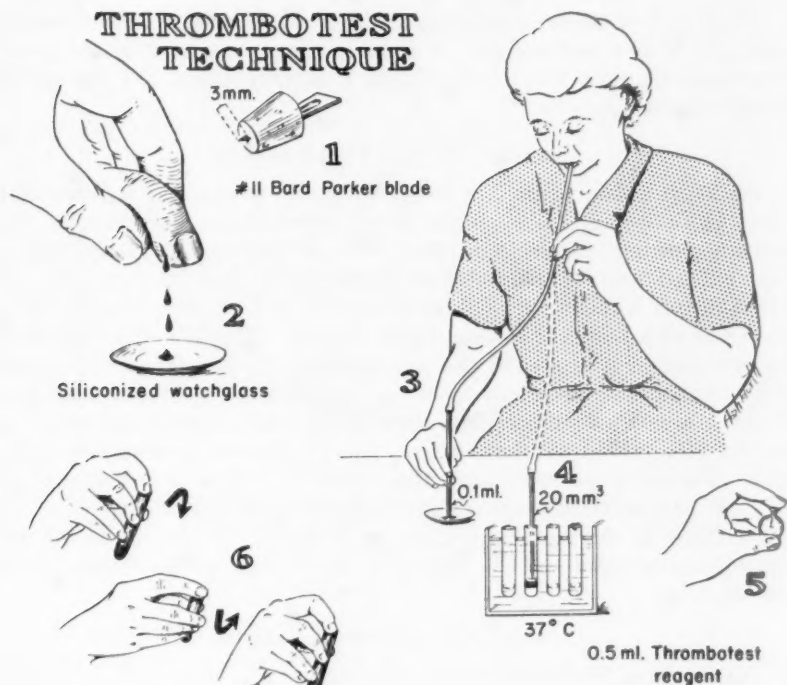


FIG. 3. Thrombotest technic.

can be performed and results be available for anticoagulant dosage control by the physician within five minutes of the patient's arrival.

A control curve of activity prepared by serial dilution of siliconized human capillary blood is provided with each lot of Thrombotest reagent. This curve, plotted on log-log scale, is illustrated in figure 2. Note that sensitivity is greatest in the steep slope between 10% and 43%, the difference in time between these two values being approximately 90 seconds, while from 43% to 100%, the clotting time difference is only 12 seconds. To facilitate accuracy in the higher range of values ( $> 43\%$ ), therefore, a 20 mm.<sup>3</sup> sample is taken instead of a 0.1 ml. sample to dilute the activity and make the reading in the steep slope of the curve. This reading in per cent is then multiplied by 4.3 to calculate the plasma value. If the 0.1 ml. sample value is less than 43%, a 20 mm.<sup>3</sup> sample dilution need not be run.

In our original evaluations, we ran duplicate capillary blood determinations from separate stab wounds on the lateral aspect of the fourth finger on the right and left hands of each patient. The paired samples agreed so closely (standard deviation =  $\pm 2.7\%$  of the mean) that duplicate determinations were discontinued.

From each of the same patients, a siliconized, citrated sample of venous blood was drawn and the plasma from this was examined in the Quick thromboplastin time system, the P and P activity assay, and the partial thromboplastin time test.

#### TECHNIC OF THE THROMBOTEST

As illustrated in figure 3, a free-flowing stab wound was inflicted with a No. 11 Bard-Parker blade in the lateral aspect of the fourth finger. To facilitate pipetting, the drops of blood were collected on a siliconized watch-glass. To 0.5 ml. of Thrombotest reagent which had been in a 37° C. waterbath for a minimum of three minutes, a 0.1 ml. sample of capillary blood was added and the stopwatch was started. The tube was tilted until the time end-point of a solid clot was reached. If this determination was 43% or greater as computed from the control curve by direct reading, a 20 mm.<sup>3</sup> sample was drawn into another calibrated pipette and added to another tube of Thrombotest reagent, and the time of clotting was measured. The value was then read from the control chart and multiplied by 4.3. This value, usually significantly higher than the 0.1 ml. sample result, was utilized as the more nearly correct estimate. If the initial 0.1 ml. sample determination was less than 43%, no 20 mm.<sup>3</sup> sample determination was done.

#### OTHER TEST SYSTEMS EMPLOYED

All tests were carried out at 37° C.

The *P and P assay system* was that described by Owren and Aas,<sup>6</sup> with the exception that barium sulfate adsorbed bovine plasma was used as the substrate. The test system consists of the following:

- 0.2 ml. of test plasma diluted 1:10 with diluting fluid II,
- 0.2 ml. of thromboplastin (saline extract human brain),
- 0.2 ml. of BaSO<sub>4</sub> adsorbed bovine substrate plasma,
- 0.2 ml. of calcium chloride 30 mM.

The *thromboplastin time* was performed as described by Quick,<sup>2</sup> except that the same saline extract human brain thromboplastin was used as employed in the P and P activity assay. Test system:

- 0.2 ml. of test plasma undiluted,
- 0.2 ml. of thromboplastin,
- 0.2 ml. of calcium chloride 25 mM.

The *partial thromboplastin time*<sup>7</sup> used as the partial thromboplastin a crude human brain cephalin suspension prepared with minor modification by the method of Milstone.<sup>8</sup> Test system:

- 0.2 ml. of test plasma undiluted,
- 0.2 ml. of cephalin suspension 1:200,
- 0.2 ml. of calcium chloride 25 mM.

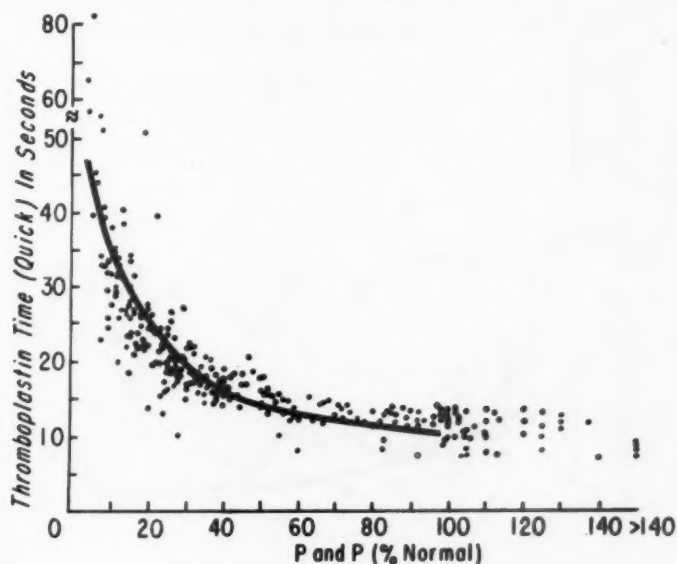


FIG. 4. Relationship of P &amp; P and Quick.

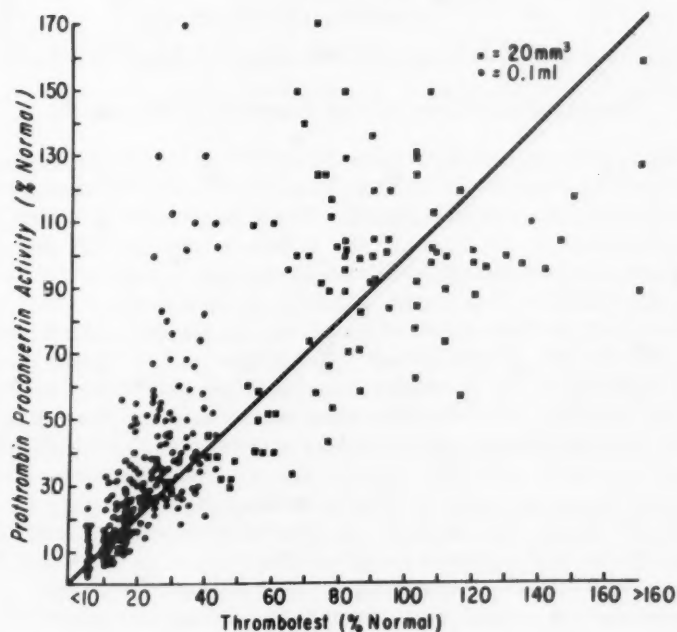


FIG. 5. Relationship of Thrombotest and P &amp; P test.

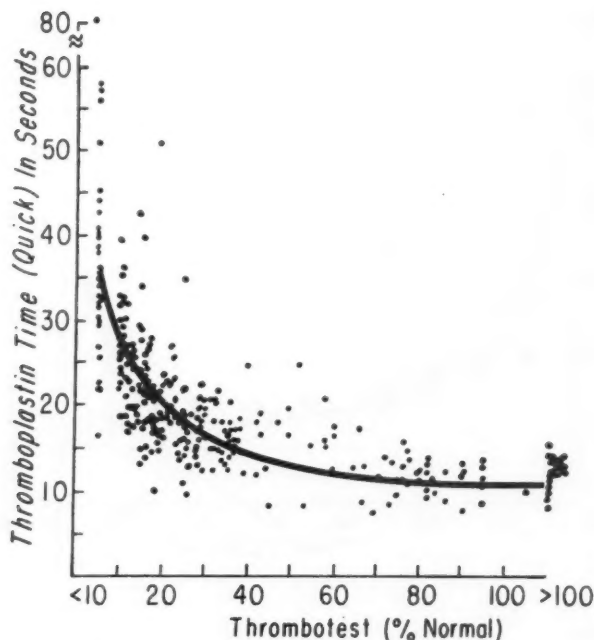


FIG. 6. Relationship of Thrombotest and Quick.

#### COMPARISON OF RESULTS BY VARIOUS TEST SYSTEMS

In figure 4 are depicted the relationships of P and P activity (in per cent) with the Quick thromboplastin time (in seconds) on the same patients, only half of whom are anticoagulated. It will be seen that the ideal range of anticoagulation in the P and P test system is between 10% and 30%; 10% P and P is roughly equivalent to 35 seconds in the Quick thromboplastin time; 20%, to 25 seconds; and 30%, to 20 seconds.

The slightly greater degree of scatter in the capillary Thrombotest as contrasted with the venous P and P test (figure 5) or Quick thromboplastin time (figure 6) is neither surprising nor particularly distressing when one considers that no corrections were made for hematocrit, and that all Thrombotests were performed by a number of individuals without previous experience with the technic. The greatest degree of agreement was in the range of values of ideally anticoagulated patients. In mock ordering of dosage, on the basis of Thrombotest results alone, dosage was usually identical with that prescribed on the basis of the P and P test result, and in no instance varied by more than one tablet per week.

Figure 6 would suggest that the capillary Thrombotest percentages are slightly lower for the corresponding value in the Quick thromboplastin



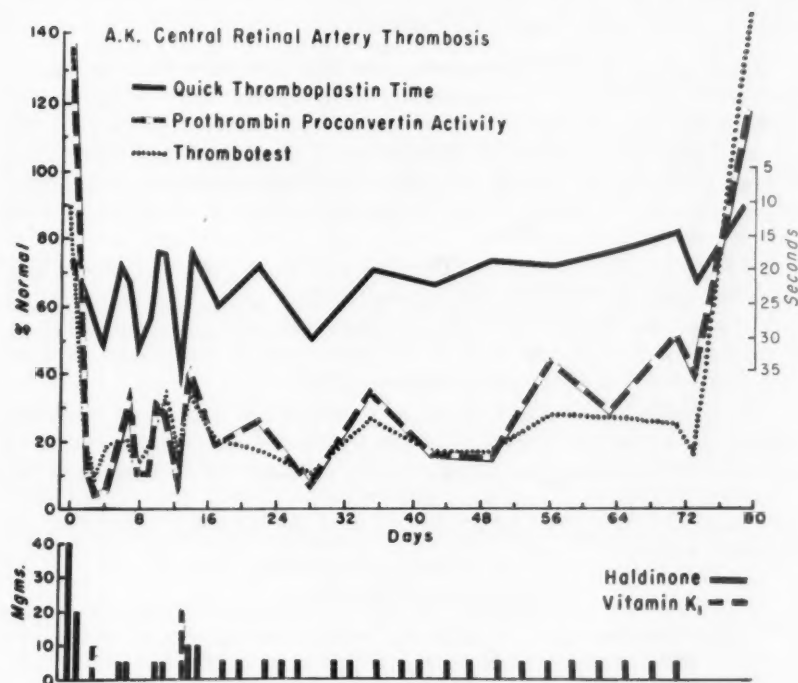


FIG. 7. Comparative values of Thrombotest, P & P test (in per cent), and Quick thromboplastin time (in seconds: right-hand scale).

time than are the P and P values; thus, 20% Thrombotest is approximately equivalent to a 20-second Quick, and a 10% to 27.5 seconds. If the P and P percent for optimal anticoagulation is 20%, the ideal Thrombotest value would seem to be 12%.

No consistent relationship was demonstrable between the partial thromboplastin time results and those of any of the other test systems described above. This may be explainable in part by the longer turnover time of PTC and the delayed expression of its decreased rate of synthesis.

As illustrated in figure 7, in a Haldinone (p-bromphenylindandione) treated patient, there was consistent parallelism of the values of all three test systems (the Quick thromboplastin time, the P and P activity, and the Thrombotest activity).

Hemorrhage as a complication occurred in only one patient during the study. This turned out to be secondary to local cause, a large, asymptomatic, preantral gastric ulcer. Bleeding occurred at a time when none of the test activities was seriously depressed. For this reason no evaluation could be made of the reported efficacy of the Thrombotest as more reliable in forewarning of serious hemorrhage secondary to anticoagulation.

## SUMMARY

The capillary blood Thrombotest described by Owren is a useful and convenient test system for regulating anticoagulant drug dosage. The Thrombotest, the P and P activity assay, and the thromboplastin time (Quick) show a fair degree of correlation. The approximate relationship between the three test systems at optimal anticoagulation levels is thromboplastin time = 25 seconds; P and P activity = 20%; and capillary blood Thrombotest = 12%.

The partial thromboplastin time shows no consistent correlation with the other three test systems, and is unsatisfactory as a guide in regulating anticoagulant therapy, though it may be prolonged after chronic overdosage. Its limitation of usefulness may be an expression of the slower turnover time of plasma thromboplastin component (IX).

The principal advantages of the Thrombotest lie in (1) its all-in-one reagent, which is diluted with distilled water and is instantly ready for use; (2) the use of capillary blood and avoidance of venipuncture; (3) the control curve specific for each lot that is provided with the reagent; (4) the availability of the equipment needed, and the easy development of the necessary skill.

## SUMMARIO IN INTERLINGUA

Le thrombotest de sanguine capillar de Owren, le test del tempore de thromboplastina de Quick, le essayo combine de activitate de prothrombina e proconvertina (P & P) de Owren e Aas, e le test del tempore de thromboplastina partial (cephalina) esseva effectuate simultaneemente in plure centenas de patientes, un medietate del quales esseva sub tractamento con drogas anticoagulante.

Le tempore de thromboplastina partial es dissatisfactori per se pro regular le dosage del anticoagulante, ben que illo pote esser prolongate per chronic excesso de dosage.

In le methodo usate, le lyophilisate reagente del thrombotest es reconstituite con aqua distillate; le libere fluxo de sanguine capillar—effectuate per un vulnere a lamina no. 11 de Bard-Parker in le aspecto lateral del quarte digito—es colligite in un siliconisate vitro de horologio; 0,1 ml de sanguine es pipettate a in 0,5 ml del reagente (que es hodie obtenibile con omne le componentes jam combine), con le precaution de un previe calefaction a 37 C; e le tempore de coagulation es determinate. Le resultados se lege directemente ab le curva logarithmic que es fornite con omne lot de reagente pro le thrombotest. Si iste valor es minus que 43%, illo es notate como resultado del test. Si illo es plus que 43%, un secunde specimen, amontante a 20 mm<sup>3</sup>, es pipettate a in un secunde tubo continente 0,5 ml del reagente, e le tempore de coagulation es determinate. Le resultado es de novo legite ab le curva de controlo e multiplicata per 4,3 pro provider un estimation plus fidel del plus alte valores. Iste mesuration dilutional es effectuate a fin que le resultados pote esser legite in le plus ardue e per consequente plus accurate portion del curva de controlo. Specimens obtenite simultaneemente ab le quarte digitos dextere e sinistre del mesme patiente produce valores con alte grados de congruitate.

Con le uso del materiales empleate in le presente studio, un test de Quick de 25 secundas es le equivalente de 20% de activitate de P & P o de 12% de activitate del thrombotest. Le ordine de valores usualmente desirate como standard de anti-

coagulation es 20 a 35 secundas in le systema de Quick. Isto representarea 10 a 30% pro le essayo de P & P e 10 a 20% pro le thrombotest.

Le avantage theoric del manovra del thrombotest es le facto que—viste que illo es un combination del tempore de thromboplastina (in que un thromboplastina non-human resulta in coagulation in circa 40 secundas con normal plasma human) con le tempore de thromboplastina partial (in que cephalina produce un tempore de coagulation sol de 50 o 60 secundas con normal plasma human)—le systema deveni progressivamente plus sensibile pro le activitate del componente thromboplastinic (IX) del plasma in tanto que le activitate de prothrombina e de proconvertina declina. Isto—theoricamente—deberea resultar in le recognition del crescente risco de hemorrhagia secundari a pharmacogene carentia de componente thromboplastinic del plasma. Infelicemente—o plus tosto, felicemente—nulle del patientes in le presente serie esseva sufficientemente hyperdosate con anticoagulantes pro permitir le observation de iste aspecto del systema del thrombotest.

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## SOME LESSONS FROM THE RED BLOOD CELL \*†

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As a teacher of medicine, I find it necessary every day to stimulate interest in the whole patient on the one hand, and in cellular structure and physiology on the other. One of the reasons the study of medicine becomes more fascinating each year is that we can now begin to sketch, albeit crudely, some probable courses of events by which abnormalities within certain cells may lead to manifestations of disease in many parts of the body. Recent studies on the red cell may be regarded as prototypes, as examples of what we may expect in the future from application of modern biochemical and biophysical methods to the study of many types of cells. Since the red cell is among the most easily sampled of all cells in the body, it is proper for us to turn to it for some lessons in cytochemistry and pathologic physiology, despite the fact that it has certain peculiarities.

### PRESERVATION OF ERYTHROCYTES IN VITRO

An awakening of interest in the red cell became apparent in the late 1930's, and has since been sparked by an increasing number of investigators, representing many disciplines. One of the first lessons learned in this new era of erythrocytology was that the red cell is a complex, highly organized, living cell.<sup>1-3</sup> The blood preservationists were among the first to teach this lesson when they demonstrated that maintenance of energy metabolism is necessary to preserve the red cell in a functional state *in vitro*.<sup>4</sup> They showed that, by the addition of dextrose to sodium citrate, the preservation of erythrocytes under the artificial conditions of storage was greatly enhanced.<sup>5,6</sup> After the addition of citric acid to lower the pH of the blood, utilization of dextrose was shown to occur over a much longer period of time,<sup>5</sup> with consequent improvement in red cell preservation. These studies led to the development of ACD (acid-citrate-dextrose) solution as we have known it since the days of World War II.

In 1954 Gabrio, Finch, Huennekens<sup>4</sup> and associates first reported that the nucleosides, adenosine and inosine, may further enhance the survival of stored red cells, perhaps by providing ribose phosphate, and thus contributing to energy production through a shunt pathway. Although the

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nature of the enzyme deficiency is not yet established. Abnormality in carbohydrate metabolism of the red cell seems likely in the light of recent studies,<sup>10, 11</sup> especially those employing radioactive phosphorus and chromatographic separation of phosphate esters involved in glycolysis.<sup>12, 13</sup> The relationship between abnormality of metabolism and abnormality of shape of the red cell remains to be determined.

Trapping of spherocytes in the spleen, on the other hand, is a feature of this disease that has been well established. This phenomenon has been demonstrated by transfusion and perfusion studies in at least four different laboratories.<sup>14-17</sup> For reasons not yet known, spherocytes are trapped more readily than normal cells, and while trapped within the splenic pulp they become thicker and more fragile. It seems likely that they become more susceptible to sequestration on each successive trip through the spleen, and that a vicious cycle may thus be established. Recent observations in our laboratory by Reed and Swisher<sup>7</sup> suggest that spherocytes may inefficiently utilize energy derived from glycolysis in maintaining the integrity of structural lipids during *in vitro* incubation. Similar loss of red cell lipids may occur when the spherocytes stagnate within the splenic pulp. The ultimate result of the splenic trapping of spherocytes is loss of integrity of the red cell and hemolysis, the consequences of which are familiar, and are indicated in figure 1 only by the arrows at the bottom of the diagram. Splenomegaly, which usually develops in this disease, is another consequence of red cell trapping.

I find it helpful to construct diagrams such as this to indicate what is known and what is unknown about the pathogenesis of various diseases that we encounter in our wards and clinics. When available information is analyzed in such exercises, we usually find that there are certain facts, such as red cell trapping in this instance, which are firmly established. Certain other findings, such as those pointing to metabolic abnormality in the red cells of hereditary spherocytosis, force us to put down some big question marks. Dr. William Bean, who is one of the most perceptive medical philosophers of our day, might refer to these findings as "embryon truths and verities yet in their chaos."<sup>18</sup> Although we do not have all the answers, there is no reason why we should hesitate to set down what we do and do not know, as I have tried to illustrate in figure 1. Someone has said that "the investigator, like the turtle, makes progress only when he sticks his neck out."

In this disease, as in many, we seem to be dealing with the consequences of a series of chain reactions set off by an abnormal gene. The task of the clinician is to break this chain of events wherever he can. In the case of hereditary spherocytosis, this can be done with one stroke by removing the spleen. The abnormality that persists in the red cell throughout the patient's life is of little or no consequence, once the spleen is removed so that the cells can circulate freely without the hazard of being trapped. It is



conceivable that, if the abnormality of the red cell were better understood, it might be corrected by chemotherapy. Whether this will ever be feasible, or prove preferable to splenectomy, are interesting questions about which we can only speculate at present.

At any rate, we have here a fine example of the dividends that come from a positive attack on an inherited disease. There is a strong tendency on the part of patients and of the medical profession to be pessimistic about genetically-determined abnormalities. A little reflection should make us realize, however, that inherited abnormalities, both rare ones and common ones, constitute a tremendous challenge to the medical profession. It is heartening to see that some of the inherited abnormalities can be dealt with effectively even before the lines of pathogenesis are clearly defined.

#### DRUG-INDUCED HEMOLYTIC ANEMIA

Another hemolytic disorder in which we have an opportunity to observe the interaction of genes and of environmental factors in the production of disease is drug-induced hemolytic anemia.<sup>19</sup> This problem has been most extensively studied in Negroes and among Caucasians of Italian, Greek and Sephardic Jewish extraction.<sup>20, 24</sup> Red cells of susceptible persons hemolyze rapidly *in vivo* when primaquine and certain other aniline derivatives are administered. Available evidence points to a deficiency of glucose-6-phosphate dehydrogenase activity as the basic abnormality in the red cells of these individuals. The term "basic" has to be used here with some reservation. Presumably it is the deficiency in activity of this enzyme that is most likely determined by the abnormal sex-linked gene. Other abnormalities, such as a deficiency in reduced glutathione, are probably secondary in nature.<sup>24</sup> Despite a great deal of fascinating research on these red cells by Alving, Beutler and associates,<sup>20-24</sup> and more recently by others,<sup>21-23</sup> the ultimate mechanism by which hemolysis occurs *in vivo* in the presence of certain drugs is far from clear.

In the light of present knowledge, it seems reasonable to draw an analogy, as suggested in table 1, between the drug-induced hemolytic anemias and

TABLE 1  
Interaction of Inherited Abnormalities of the Red Cell and Environmental Factors in  
Production of Hemolysis; Analogy between Drug-induced Hemolysis and  
Hemolysis in Hereditary Spherocytosis

red cell deficient in glucose-6-phosphate dehydrogenase	+	primaquine or related drugs	→ hemolysis
hereditary spherocytosis with ? abnormality in carbohydrate metabolism	+	splenic trap	→ hemolysis

hereditary spherocytosis. In both conditions we are dealing with inherited biochemical abnormalities of the red cell that are of little or no consequence

so long as the cells are not exposed to certain environmental challenges. In the one case a drug such as primaquine, phenacetin or Furadantin provides a type of environmental factor needed to cause *in vivo* hemolysis, while in hereditary spherocytosis the splenic trap provides an environment conducive to hemolysis of the inherently defective cells. I can think of no better models to hold up to students as we consider some of the basic principles in pathogenesis of disease by interaction of heredity and environment.

#### EFFECT OF MODIFYING GENES ON THE ABO BLOOD GROUP SYSTEM

Studies on blood groups and their inheritance have provided many interesting lessons, of which I have chosen to cite two that have fascinated me most. One is the series of observations that have been made on modifying genes, which are genes detected only by their effects on the expression of other genes. It is suspected that modifying genes may be involved in producing some of the variants in the clinical manifestations of hereditary disorders. Only in the blood group substances do we thus far have clear examples to which we can point as illustrations of the effect of modifying genes in man. Recent studies on the ABO system are especially interesting, and deserve our attention.

The ABO genes are apparently capable of flooding the saliva and other body fluids and tissues with a corresponding antigen, but whether they do so depends upon the action of a pair of modifying genes, the so-called secretor genes, which have been recognized since 1932. In the non-secretors—who, it must be understood, are healthy persons—there is interference with secretion of A, B and H substances in body fluids, due either to lack of the secretor gene, *Se*, or to a double dose of the non-secretor gene, *se*, that is, the genotype *se se*.<sup>26</sup>

A remarkable genotype, named Bombay for the location of the person in whom it was first demonstrated in 1952, prevents the B and O genes from causing the formation of B and H factors both in red cells and in the body fluids.<sup>25-27</sup> The rare Bombay genotype is usually the result of consanguineous marriage. It is now customarily labeled *xx*. Persons with this genotype have naturally-occurring anti-H antibodies, and therefore cannot be transfused safely except with blood from another person of the Bombay genotype.

Still another rare and remarkable genotype, first demonstrated by Weiner and associates<sup>28</sup> in 1957, and now labeled *yy*, inhibits the development of the A antigen in red cells and to some extent in body fluids.

We shall do well to keep our eyes on the modifying genes!

#### ACQUISITION OF B-LIKE ANTIGEN BY GROUP A ERYTHROCYTES

The second lesson I wish to cite from recent studies on blood groups is the demonstration that a B or B-like antigen on red cells may be acquired.

All of the 10 persons with red cells exhibiting this phenomenon belonged to blood group A (genotype AA or AO), and most of them were either elderly or suffering from cancer.<sup>29-32</sup> These reports are startling, since we have assumed for many years that the B antigen on red cells is always determined by a gene specific for this antigen. We are learning, however, that many findings in the laboratory as well as at the bedside may be reached by more than one pathway. We learned some years ago that spherocytosis, for example, is by no means always inherited, but that it may be acquired—that is, induced by antibodies and by chemical and physical agents.<sup>9</sup> Now we learn that the B antigen may be acquired in some mysterious manner by group A red cells.

#### HEREDITARY METHEMOGLOBINEMIAS

Other examples of the multiple pathways that may be involved in the pathogenesis of a disease state are found in the hereditary methemoglobinemias. In the first type to be delineated, deficiency of an enzyme, quite likely diaphorase, is considered to be responsible for the accumulation of methemoglobin in the red cells of affected persons.<sup>33-36</sup> This abnormality appears to be transmitted recessively in most, but perhaps not in all, afflicted families.<sup>37-39</sup>

More recent studies have revealed another form of hereditary methemoglobinemia, in which the hemoglobin molecule itself is abnormal, and is somehow associated with faulty reduction of heme.<sup>40-43</sup> There is no deficiency in any of the enzymes studied in the red cells of these persons.<sup>43</sup> It now appears that the abnormal hemoglobin found in the red cells of the families studied to date are of four different types, each of which is transmitted dominantly.<sup>47, 49</sup> Differences among these abnormal hemoglobins are revealed by spectroscopy and electrophoresis. It has been suggested by Gerald that these types of hemoglobin M be labeled provisionally as B, M and S, for the names of the cities—Boston, Milwaukee and Saskatoon—in which reside the afflicted families first studied.<sup>47-49</sup> The fourth type, recently identified by Gerald and George,<sup>47, 49</sup> is thus far nameless.

#### DEMONSTRATIONS OF HETEROGENEITY

Thus we have in the red cell another fine example of the demonstration of heterogeneity in a state that was thought to be homogeneous—that is, hereditary cyanosis associated with methemoglobinemia. This is part of a pattern that is becoming familiar as modern laboratory technics are applied in studying various types of specimens provided by patients and their relatives. A remarkable degree of heterogeneity has been demonstrated recently with respect to blood group antigens,<sup>25</sup> spherocytosis,<sup>50</sup> thalassemia,<sup>9</sup> hemoglobinopathies<sup>9</sup> and methemoglobinemias. The red cell seems to be leading the parade of such demonstrations. This is another way of saying that

progress in medicine is dependent in large part upon more and more precise characterization of biochemical abnormalities or variations. As of today, the red cell no doubt provides us with more examples of this type of progress than does any other cell of the body. The ultimate objective of such progress is presumably the characterization of each variant in terms of molecules or parts of molecules, as achieved most brilliantly to date in certain of the hemoglobinopathies.

#### DEFECTIVE TRANSKETOLASE REACTION IN RED CELLS IN WERNICKE'S SYNDROME

Another type of study recently conducted on red cells is the demonstration in these readily accessible cells of biochemical deficiencies affecting other tissues as well as the red cells. A good example is the defective transketolase reaction found in red cells of patients with ophthalmoplegia as a feature of Wernicke's syndrome, a condition due to thiamine deficiency and encountered chiefly in alcoholics.<sup>51, 52</sup> This finding is presumably due to the fact that thiamine pyrophosphate is a co-factor for the transketolase reaction. It is thus possible to demonstrate evidence of thiamine deficiency in the readily sampled red cells without having to resort to chemical study of the nerve cells, in which thiamine deficiency is actually causing symptoms.

#### ENZYME DEFICIENCY IN RED CELLS IN GALACTOSEMIA

I wish also to invite your attention to recent studies on galactosemia, an inherited condition characterized not only by galactosemia but also by cataracts, hepatomegaly, jaundice, amino-aciduria, mental deficiency and stunted growth. A deficiency in galactose-1-phosphate uridyl transferase has been demonstrated by Schwarz and associates<sup>53, 54</sup> and by Isselbacher, Anderson, Kalckar and associates,<sup>55-58</sup> both in the liver and in red cells of patients with this type of inborn metabolic error. The mechanisms responsible for impaired function of nerve cells, as reflected in mental deficiency, and for impaired function of liver and kidney, are not yet clear. Deficiency of the transferase does not appear to alter the shape or the life span of the red cells, but a decrease in adenosine triphosphate in the red cells was noted in one patient by Pennington and Prankerd,<sup>59</sup> and was corrected after removal of galactose from the patient's diet. It seems possible that further studies on the intermediary carbohydrate metabolism of the readily accessible red cells in galactosemia will help to reveal the nature of the metabolic derangements of the brain, liver and kidney cells in this disease. Assay of transferase in red cells is already accepted as a highly sensitive and specific method of detecting this disorder.<sup>57</sup>

#### DECLINE OF ENZYME ACTIVITY WITH AGE IN CIRCULATING RED CELLS

Before closing, I wish to turn to still another biologic arena in which studies on the red cell are providing information of considerable interest.

One of the most challenging of all biologic puzzles is that of aging. It seems logical to explore the aging process in many forms of life by demonstrating changes that occur with age in individual cells. The life span of the red cell has been measured accurately in recent years in many species, and under both normal and pathologic conditions.<sup>9</sup> Probably no other type of cell has been subjected so frequently to measurements of this type. It is well accepted that the life span of the normal human red cell is about 120 days.

Studies by Allison and Burn<sup>60</sup> and, more recently, by Marks and associates,<sup>61</sup> Löhr et al.<sup>62</sup> and Bernstein<sup>63</sup> have shown that the activity of the following enzymes present in the human red cell declines as the cells age in the circulation: glucose-6-dehydrogenase, 6-phosphogluconic dehydrogenase, phosphohexose isomerase, aldolase, catalase, glyoxalase and cholinesterase. It seems likely that loss of enzyme activity and consequent deficiency in energy production lead ultimately to death of the cell. Although we must be cautious in translating findings in the non-nucleated, specialized red cell to other types of cells, we may nevertheless argue that the studies on aging of circulating red cell populations have contributed significantly to our current understanding of cellular aging.

#### STUDIES ON RED CELLS OF THE AGED

So much for the aging of individual cells! What about the structure and metabolism of red cells of elderly people or animals? Do they differ from the red cells of younger members of the species? These questions cannot yet be answered in definitive terms. Differences have been reported by Goldschmidt<sup>64, 65</sup> in resistance of red cells to lysis by heat, the cells of older persons and animals being less resistant. Since red cells are so easily sampled, and since precise methods of study are now available, it would seem distinctly worth while to explore the finer cytochemistry and metabolism of red cells from subjects of various ages. This is one avenue for investigation of aging that appears to be wide open at the present time.

I trust you will agree that the pace of research on the red cell during the last two decades has been phenomenal. It seems safe to predict that within these remarkable and readily accessible cells many more noteworthy discoveries remain to be made. I like to regard the erythrocyte as a key cell, because it can be used advantageously to unlock some of Nature's most fascinating puzzles.

#### SUMMARIO IN INTERLINGUA

Le erythrocyto es un complexe e altamente organisate cellula vive que ocasiona le apprension de multe lectiones de physiologia cellular, de genetica, e de pathogenese.

Le preservationistas de sanguine esseva inter le primes qui signalava le requirimento de un continue production de energia intra le erythrocyto pro le mantenentia

del viabilitate cellular. Disturbationes del metabolismo intra le erythrocytos esseva solo recentemente recognoscite como factores essential in le pathogenese de certe statos hemolytic. Es notate particularmente le entitate de spherocytosis hereditari e le anemias hemolytic de classe pharmacogene que ambe es illustrationes classic del interaction de hereditate e ambiente in le genese de maladia. In spherocytosis hereditari, le splen provide un ambiente disfavorabile resultante in le destruction de inherentemente defective erythrocytos. In subjectos susceptible de suffer hemolyse pharmacogene, le anormalitates biochimic del erythrocytos non es manifeste usque le cellulas es provocate per certe drogas, como per exemplo primaquina.

Ab le puncto de vista del gruppos de sanguine, duo importante lectiones es citate. Un es le rolo de tres pares de genes modificatori in le mecanismo de expressivitate del genes A, B, e O, le quales determina le disveloppamento del antigenos A, B, e H in everythrocytos e fluidos del corpore. Le secunde es le interessante evento del recente demonstration del acquisition de antigeno B per erythrocytos de gruppo A in certe subjectos, generalmente de etate avantiate e/o suffrente de cancro. Iste constatacion es un exemplo del multiple vias per le quales un substantia particular pote esser producite o acquirite per le corpore.

Currentemente le erythrocyto es al capite del parada de demonstrationes de heterogeneitate o de differentiation inter statos anormal que prevemente esseva considerate como homogenee. Fascinante exemplos es a trovar inter le hemoglobino-pathias, in le methemoglobinemias hereditari, in spherocytosis, e in thalassemia. Le ultime objectivo de tal demonstrationes de heterogeneitate es le identification de anormalitates intra le cellula al nivello molecular.

Certe anormalitates metabolic que es commun al erythrocyto e al altere cellulas del corpore pote esser demonstrate multo plus facilmente in le erythrocyto proque le prisa de specimenes de illo se effectua plus facilmente. Excellente exemplos de isto se trova in le area del carentia de thiamina e de galactosemia.

Un altere arena biologic in que studios del erythrocytos provide resultados de interesse es le rapidamente crescente dominio del investigationes del processo invetulatori. Viste que—presumemente—le invetulation debe esser explicate in parte al nivello cellular e viste que le erythrocytos inter omne le cellulas del corpore es le plus facilmente a speciminar, le recente studios del invetulation de populationes de erythrocytos e del differentias que occorre in erythrocytos in relation al etate del donator es digne de nota.

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## OBJECTIVE EVIDENCE OF THE STATE OF ACQUIRED VALVE LESIONS OBTAINED WITHOUT TRAUMA BEFORE AND AFTER SURGERY \*†

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OBJECTIVE criteria of the results of therapy permitted the development of effective management for tuberculosis, pernicious anemia, diabetes and prostatic cancer, while false hopes had been aroused by enthusiasts or quacks whose claims for cures of consumption or cancer were based on the sense of well-being in their patients, with no objective evidence of control of the disease. For physicians familiar with the contrasting histories of effective management and bogus cures, it was disturbing to note the emphasis on how well patients felt after mitral valvotomy, and the absence of objective evidence of change in cardiac function in most reported series of patients.

In congenital heart disease, when shunts are closed during open-heart surgery, there is no more question of the effectiveness of the procedure than there would be about removal of an appendix. But when valvular insufficiency or a stenotic lesion is attacked, or a ligature is put around a patent ductus, it obviously is wise to obtain objective evidence of the resulting change in the circulation to decide whether treatment has been curative, palliative or ineffective. Data on survival are not decisive, since there is no proof that the groups that have been operated upon and those that have not were identical at the start.

The failure to use objective data in control of the operation for mitral stenosis explains why thousands of patients all over the world were subjected to Souttar's procedure, finger fracture, before the men who had most experience began to realize that the operation was as undependable as Souttar's critics had surmised. Now Harken speaks of doing a valvuloplasty, Bailey attacks from behind the right atrium, others turn to open-heart valvular repair, and the Scottish surgeons report nearly 500 patients in whom dilators were introduced through the left ventricle. All of these men are using technics involving higher operative mortality in order to get better end results. Finger fracture made many patients "feel better," but actually had

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little effect on the mitral orifice in the majority of patients. This would have been realized years ago if proper objective methods of evaluation had been used before and after operation.

Ideally, all stenotic or insufficient valves should be studied by simultaneous measurements of pressure gradients and flow volumes, at rest and after exercise, before and after operation. Angiography, cine-angiography, and dye dilution curves give less quantitative but very useful information on valve function, after the tracer is injected into the ventricles, aortic root and right atrium. Study by catheter and angiography has made possible a great advance in understanding of all forms of heart disease, and made diagnosis in individual cases even more precise than that provided by morbid anatomy. But even those who use these methods routinely before operation realize that patients will not accept the hazard and discomfort of repeated study in the years after operation. Although preoperative evaluation became more dependable, the postoperative course remained obscure, and subjective status was stressed rather than objective data.

There are, however, a number of less precise but satisfactory objective methods for evaluating these lesions. The oldest and simplest is to record the heart sounds. Such records bear the same relation to study of valve lesions that chest films bear to auscultation or fluoroscopy of the lungs. This method has not been applied in many clinics where hundreds of mitral valves have been attacked, although the specific changes related to mitral stenosis have long been studied. Delay in onset of first sound and the interval between second sound and snap are closely related to gradient of pressure between atrium and ventricle.<sup>1,2</sup> It is change in these time relations, rather than in the murmurs, which helps us evaluate mitral lesions after surgery. Many variables—heart rate, stroke volume, myocardial weakness, calcification of valves—may modify these relations and must be considered before drawing conclusions. But phonocardiography provides permanent objective data in place of recollections of the heart sounds; and heart sound records, when read in the light of clinical findings and of the methods described below, make an invaluable part of the postoperative study.

Roentgen study by slit kymography may give a permanent record of the calcification of valves,<sup>3,4,5</sup> and one more sensitive and reliable than is fluoroscopic observation (figure 1). The presence of mitral calcification is not revealed by angiograms or catheter studies, and yet it may explain the absence of snap and diastolic murmur in otherwise typical cases of mitral stenosis. Calcification also may influence our decision as to whether to operate, or what operative approach to use. The slow filling of the left ventricle, best shown in the left anterior oblique kymograms, provides striking proof of inflow obstruction. Since the left ventricle fills swiftly in mitral insufficiency, in myocarditis and other types of disease causing congestive failure, and in young people with third heart sounds, changes in filling curve after operation may give proof of change in the size and sufficiency of the

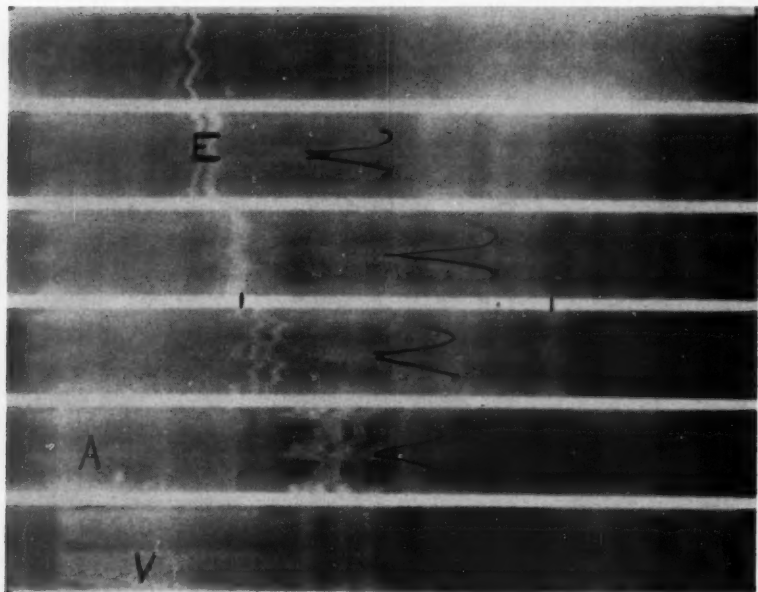


FIG. 1. From a man, age 34, with typical mitral heart except for very faint opening snap and diastolic murmur. The slit kymogram, right anterior oblique, shows chalk in the mitral valve or annulus in four frames (anterior edge inked in for one beat). E, barium in esophagus moves with aorta in top frame, with left atrium in third and fourth frames. A, right atrial border; V, right ventricle, filling swiftly in early diastole. The motion of the mitral valve is always much greater than that of any heart border. It is opposite in direction to the apex and left ventricular border. The left atrium moves with the annulus. This calcification could not be seen at fluoroscopy.

orifice. Gradual reversion to the preoperative pattern of this curve, and of the time relations of first sound and snap, speaks for restenosis. The slow filling of the left ventricle, characteristic of mitral stenosis, may be concealed by a huge right ventricle and tricuspid insufficiency. It may be simulated by low venous return if the patient holds his breath too long before the film is exposed.<sup>6</sup> Only meticulous technic yields dependable data.

Up to 30 years ago, secretaries of societies who had invited me to give lectures usually turned down titles which dealt with that mysterious device, the electrocardiograph. In the last 10 years I have found that discussions of the ballistocardiograph were equally unpopular. Most cardiologists, young or old, have for this simple gadget, which gives evidence on how fast blood enters and leaves the ventricles, the same contempt that Sir James MacKenzie had for the electrocardiograph. And for the same reason—they have never used it. The three-plane ballistocardiogram is as useful in studying mitral disease as the 12-lead electrocardiogram is in the study of myocardial infarction. Since most ballistocardiographers seek a clue to stroke volume or myocardial force, and use only Starr's head-foot trace,



they miss as much information as would electrocardiographers if they recorded only Lead II because they were interested only in cardiac rhythm.

In valvular disease and heart failure, lateral and dorsoventral curves may be markedly abnormal when the head-foot trace is normal. One striking feature of mitral stenosis is the small size of diastolic waves, while giant waves occur in mitral insufficiency, myocardial failure and constrictive pericarditis.<sup>7,8</sup> I would be discouraged by the fact that the pioneers in ballistocardiography are uninterested in our three-plane records if I did not remember that, in 1925, Sir Thomas Lewis and Karl Wenckebach, the pioneers in electrocardiography, threw very cold water on my confidence in the importance of the S-T changes noted in coronary disease. That aspect of electrocardiography, described in 1918 by my teachers James Herrick and Fred Smith, was widely ignored for a decade. In the end the "stone that the builders refused has become the head stone of the corner." A similar change in attitude to three-plane ballistocardiograms is not impossible.

Records of jugular, carotid, precordial and electrokymographic pulses may also be helpful in evaluating valve lesions and their modification by operation.<sup>7, pp. 2-11</sup> We have recorded sound and pulse curves for over 30 years, slit kymograms for 15 years, and three-plane ballistocardiograms for seven years. For the last decade we have been able to compare our findings with catheter and angiocardiographic data or surgical exploration, as well as necropsies. We have repeatedly used these painless and harmless methods to record the effects of exercise, Valsalva's experiments and drugs on our own hearts. Catheter study has taught us much about the sources of error in interpreting these findings, and especially about the jugular pulse curves. As with all diagnostic procedures, poor technic or poor coöperation of the subject may spoil the records, and multiple lesions or intercurrent disorders (anemia, uremia, Graves' disease or fever) may render "experience fallacious, judgment difficult."

Use of these atraumatic methods for study of the heart makes angiograms or catheter studies of no additional value in most mitral cases, and

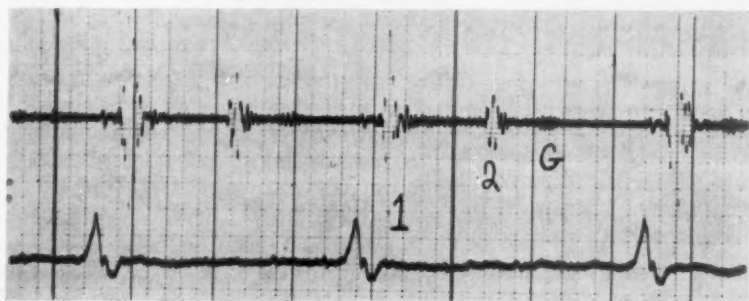


FIG. 2. Heart sounds of a man with a large heart, proved at necropsy to have a rigid mitral valve with a large orifice. The loud late first sound and the soft protodiastolic sound, G, fitted mitral stenosis; the systolic murmur was not loud.

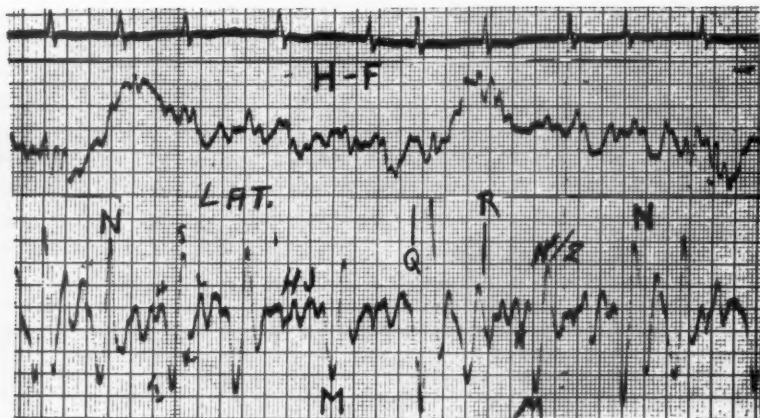


FIG. 3. The head-foot ballistocardiogram of case in figure 2 shows small, chaotic waves, but the lateral trace shows huge, protodiastolic M N waves. These are recorded at half of the usual galvanometer sensitivity. The small letters H J K L on third beat were due to erroneous interpretation. After short diastole (as in beat with Q), protodiastolic and systolic forces are superimposed and mimic systolic I J waves. With long diastole, the classic giant M N waves of mitral reflux are clearly seen.

provides a dependable check on the result of operation. In aortic valve disease and combined lesions, catheter study is more often needed before deciding whether to advise operation. Failure to use atraumatic tests in cases subjected to catheterization or angiography has led to serious misinterpretation of data even in our own clinic. We have encountered far more of these errors in patients studied elsewhere. Wedge pressures led other groups to explore the mitral orifices of patients with pure myocarditis, and this even happened to one case of healed infarction. In all of these

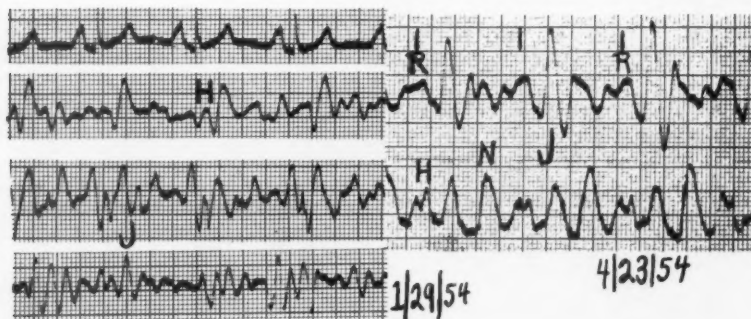


FIG. 4. From a young woman with signs of mitral and aortic stenosis, and right heart failure. Preoperative tracing (1/29) shows small systolic force in all planes, and a large presystolic rightward wave. After mitral valvotomy there were much larger systolic forces (J) and a tall, broad protodiastolic lateral wave, suggesting myocardial damage or mitral reflux (4/23). The presystolic wave, seen in mitral and in tricuspid stenosis,<sup>9</sup> has become smaller.

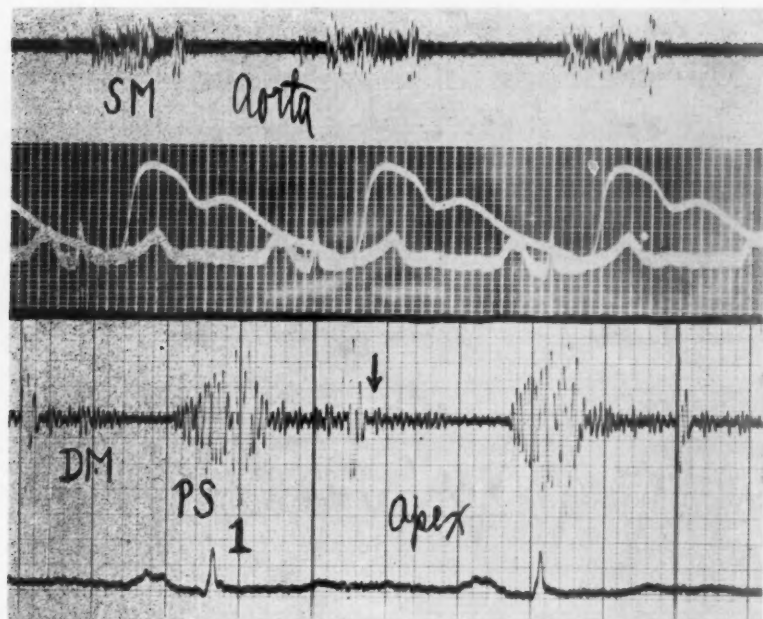


FIG. 5. Same case, three years later, in complete clinical remission. There is an aortic systolic murmur, SM. The brachial pulse is within normal limits but compatible with aortic stenosis. The presystolic and diastolic murmurs are about as they were before operation; the faint opening snap is 0.07 sec. after second sound, and was 0.05 sec. before operation, suggesting fall in left atrial pressure.

cases, gallop was mistaken for diastolic murmur. In another case, the wedge pressure pattern was interpreted as proving mitral insufficiency, but the slit kymogram showed that the convex upper left border all moved as aorta, with an incisura identical with that at the knob. Aneurysm of the sinus of Valsalva in this typical case of Marfan's syndrome, and aortic insufficiency in others, produced large c-v waves in wedge pressure curves because the left auricle surrounded the root of a vigorously expanding aorta. In one of our patients, a faint sound in diastole, a high wedge pressure and absence of a systolic murmur persuaded a novice in our group to ignore giant diastolic ballistocardiographic waves. Instead of mitral stenosis, free mitral regurgitation was found at operation and necropsy (figures 2 and 3). These experiences convince us that evaluation of all of the evidence available from cheap and harmless studies is the least a patient deserves before we can determine the need for more disturbing tests, or for an operation.

It is now becoming clear to most internists, as it has been to us for 10 years, that definitive surgery for acquired heart disease has yet to be developed. Even the latest procedures are palliative at best, and often in-

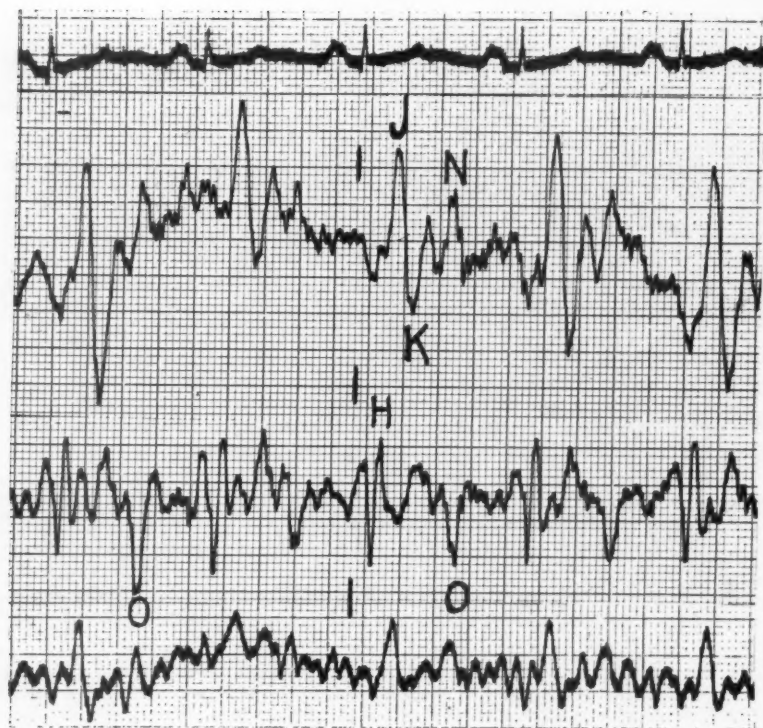


FIG. 6. Same case, six years after operation, in complete clinical remission. The large systolic ballistocardiographic waves in three planes indicate normal volume and velocity of ejection. The protodiastolic waves, swift and at upper limit of normal, suggest minimal mitral reflux and swift early diastolic inflow. In this case, the ballistocardiogram foretold a good outcome when heart sounds suggested little effect from surgery.

effective. Since the most experienced groups have devised very different technics for dealing with mitral stenosis, in every case objective data on heart sounds and ballistocardiograms should be recorded to serve as a base line for postoperative evaluation (figures 4, 5, 6). Had this been done in the thousands of mitral patients who submitted to operation in the last decade, the value and shortcomings of Souttar's operation would have been defined long ago, and progress in cardiac surgery would have been far more rapid.

Most patients believe that the risk and discomfort of thoracotomy would not be advised unless an operation is almost certain to cure their disease. They will accept painful and expensive diagnostic procedures as necessary preludes to operation. Very wisely, they avoid repetition of these procedures at intervals after surgery. To control what treatment is doing, we must learn to use the right tools, and especially technics which our patients can accept cheerfully for repeated examinations.

Because the outcome of operation for acquired valvular disease is not predictable, and methods are still being evolved to improve their effectiveness, the internist must decide whether a patient's disability is serious enough to justify immediate operation, or whether surgical technics are likely to get better faster than the patient will get worse. The indications may be different for a solitary person with a fixed income and for a disabled wage-earner with dependents. In the case of a mother with young children, prolonged survival, made possible by ideal dietary and medical control, may be invaluable in protecting a home from disintegrating. When all of the diagnostic tests have been carefully weighed, the personality and obligations of the patient must be fully considered if we are to adhere to the rule of *Primum non nocere*, "Above all, do no harm."

#### SUMMARIO IN INTERLINGUA

Catheterismo cardiac e angiocardigraphia ha promovite nostre cognoscentias de acquirite morbo cardiac e le precision de nostre diagnoses, sed ille methodos non es appropriate pro le repetite studios que es necessari in evaluar le resultados de valvulotomia. Methodos plus traditional—per exemplo phonocardiographia e kymographia a fissura—pote esser repetite sin disconforto e sin risco, e illos es ben capace a producer evidential objective de alterationes functional. Ballistocardiographia triplanar—producente evidential de alterationes del ejection in le grande vasos e etiam del intensitate del influxo ventricular in diastole—se ha provate de grande valor in le differentiation inter stenosis e insufficiencia mitral e etiam in le demonstration de quanto frequentemente le function cardiac remane essentialmente inalterate post le fractura digital del valvula mitral. Stenosis mitral con calcification ha minus frappante clics de apertura e murmures diastolic. Iste alteration es revelate per kymographia a fissura ante que illo deveni evidente per fluoroscopia.

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## THE INFILTRATION OF CAROTENOIDS INTO HUMAN ATHEROMAS AND XANTHOMAS \*

By DAVID H. BLANKENHORN, M.D., *Los Angeles, California*

CAROTENOIDS are lipids which are usually colored either red or yellow. In figure 1, the distinguishing characteristics of the carotenoid molecule are illustrated by the specific carotenoid lycopene. Common to all carotenoids is a long central carbon chain which contains a sequence of periodic double bonds and methyl side groups. In certain carotenoids, the ends of this chain are closed rings. Other carotenoids have a hydroxyl group attached to the terminal ring, and may occur in nature either as the free carotenoid alcohol or as the ester of a fatty acid. Carotenoids occur in human tissue as a result of absorption from the intestine of pigments ingested with foodstuffs. There is abundant evidence that carotenoids are not synthesized by any human tissue. Because certain carotenoids serve as precursors of vitamin A, studies have been performed to determine the effect of a carotenoid-free diet in normal man. When carotenoids are omitted from the diet, blood and tissue levels promptly decline, and continue to fall until carotenoids can no longer be detected.<sup>1</sup> On the other hand, increased carotenoid intake promptly leads to an increase in blood and tissue levels in persons with normal intestinal function.<sup>2</sup> Contrary to older belief, carotenoids in blood are not merely dissolved in the other lipids of blood, but each is transported by a specific carrier system as lipoproteins. The majority are transported with lipoproteins having ultracentrifugal behavior of the SF 3-9 class.<sup>3</sup> It is important to realize that only trace amounts of carotenoids are found in human blood. A normal value for serum carotenoids is in the neighborhood of 20  $\mu$ g. per 100 c.c. This is a concentration only 1/10,000 that of a usual cholesterol level in normal serum. Because carotenoids occur in such small amounts and are responsive to changes in diet, these pigments offer a unique opportunity for clinical investigation. Blood levels of these pigments can be manipulated almost at will without affecting other serum lipids and without deranging the over-all economy of lipid metabolism.

Some of the highest concentrations of carotenoids in human tissue occur in atheromatous lesions and in xanthomatous tumors. Xanthomas are lipid-filled tumors seen in certain patients with disordered fat metabolism. They have received the name "xanthoma" because of the yellow color im-

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parted to them by carotenoids. (At one time, the term "xanthophyll" was used in place of the term "carotenoid" as a generic name for this class of pigments. At present, xanthophyll is reserved for a specific carotenoid, 3, 3'-dihydroxy-alpha carotene.) High concentrations of carotenoids are also found in the adrenal gland, the ovary and the retina; lesser concentrations of carotenoids are found in depot fat and liver. Because of the size of the depot fat stores and the liver in normal man, these are the major sites of carotenoid storage. Total body stores of carotenoids have been estimated to vary from 50 to 300 mg.<sup>4</sup> In all, 10 different carotenoids have been isolated from human tissue (zeta carotene, alpha carotene, beta carotene, prolycopene, lycopene, cryptoxanthin, xanthophyll, zeaxanthin, capsanthin and capsorubin).<sup>5, 6, 7</sup> Three of these can serve as precursors of vitamin A (alpha carotene, beta carotene and cryptoxanthin).<sup>8</sup>

The selection of carotenoids found in human tissue depends upon the habitual diet of the individual, and can therefore show variation due to racial and cultural peculiarities. The tissues of Hungarians are reported to contain two rare carotenoids—capsanthin and capsorubin—which occur in

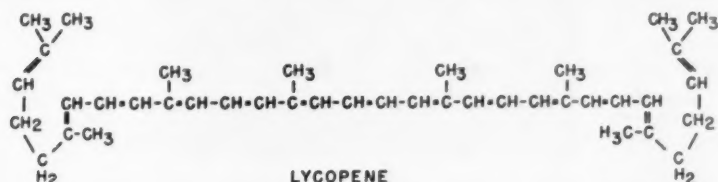


FIG. 1. The structural formula of lycopene ( $C_{40}H_{56}$ ), one of the more common carotenoid pigments.

paprika.<sup>6</sup> Residents of southern Ohio store zeta carotene, alpha carotene, beta carotene, prolycopene, lycopene, cryptoxanthin, xanthophyll and zeaxanthin. The predominant pigments of Ohians are beta carotene, lycopene and xanthophyll.<sup>7</sup> In addition to variation caused by diet, serum carotenoid levels are known to be elevated in diabetes mellitus,<sup>9</sup> myxedema,<sup>10</sup> familial carotenemia<sup>11</sup> and familial hypercholesterolemia.<sup>12</sup> Blood carotenoid levels are depressed in persons with intestinal malabsorption, cirrhosis, pancreatitis,<sup>2</sup> thyrotoxicosis<sup>10</sup> and acute febrile states,<sup>8</sup> and in normal individuals on a carotene-poor diet.

It has long been known that carotenoid pigments are responsible for the yellow color of early atheromas.<sup>13</sup> Recent work indicates that advanced atheromas also contain these pigments, although their color may be masked by overgrowing fibrous tissue. If this fibrous tissue is extracted with fat solvents, the presence of carotenoids is easily demonstrated. Systematic investigation of the carotenoid content of human atherosclerosis indicates that a steady increase in carotenoids occurs as atheromas grow and become more severe.<sup>14</sup> Data obtained by chemical assay of a series of 52 aortic

segments exhibiting atheromas of varying size and severity are shown in table 1. These aortas were taken from 30 unselected patients who died of various diseases and came to autopsy in a large general hospital. Grade I lesions were those which, on gross examination, showed only the first signs of intimal thickening or pale translucent plaques. Grade II lesions were yellow, opaque, discrete plaques. Grade III lesions were thick, gray-white and often confluent, and showed evidence of fibrosis and some calcification. Grade IV lesions were more severe than Grade III, and usually showed ulceration and extensive calcification. The schema of grading employed to classify these lesions has been described in more detail.<sup>14</sup> Examination of table 1 shows that the carotenoid content increases steadily as lesions advance from Grade I to Grade IV. Cholesterol is the major lipid component of atheromas and, for comparison, the cholesterol content of these segments is also shown. Because carotenoids accumulate as rapidly as cholesterol, an essentially constant ratio results. It may be of significance that the value found in atheromas is quite close to the carotenoid/cholesterol ratio found in serum.

TABLE 1  
Carotenoid Content of Aortic Atherosclerosis

Severity of Atherosclerosis	Total Epiphasic Carotenoids, $\mu\text{g./cm.}^2$	Total Cholesterol, $\text{mg./cm.}^2$	Carotenoids, $\mu\text{g.}$ Cholesterol, $\text{mg.}$
1	.04	.31	.13
2	.10	.71	.14
3	.24	1.4	.16
4	.65	3.9	.17

(Reprinted from the *Journal of Clinical Investigation*.<sup>14</sup>)

A second means to demonstrate the presence of carotenoids in atherosclerotic lesions is by fluorescence microscopy. When fresh-frozen sections of atheromatous lesions are examined by ultraviolet light under the microscope, they exhibit a variety of fluorescent colors. Carotenoid pigments produce pale blue-green fluorescence and a dull, dingy green fluorescence which may fade after a few minutes' exposure to ultraviolet light. Often the more brilliant fluorescence of other constituents of the atheroma may obscure that due to carotenoids. However, with care these pigments can be found in most fresh unfixed atheromas.<sup>15</sup> With this technic, carotenoids are found scattered unevenly and at random throughout all of the lipid-bearing parts of atheromas (figures 2 and 3). Only small amounts of carotenoids are seen in early lesions, but an abundance is present in advanced lesions. These microscopic findings are in complete accord with the results of chemical assay.

Another aspect of abnormal lipid metabolism which can be investigated using carotenoid pigments is the manner in which lipid accumulates in



FIG. 2. Detail from the edge of an atheroma. Hematoxylin and Sudan IV. In the upper left corner, uninvolved media is present. Fat-laden atheroma, heavily stained with Sudan IV, is seen elsewhere.

xanthomatous tumors. The most common of the abnormal states which may produce xanthomas are diabetes mellitus, familial hypercholesterolemia and biliary cirrhosis. To date, only the xanthomas of a patient with diabetes mellitus have been studied. The opportunity for this study presented when a 77 year old Negro man with mild diabetes mellitus requested the removal of a large ulcerated tumor from one buttock. He had been a known diabetic for 25 years but did not take insulin and had only mild glycosuria. On his buttock a tumor had been growing slowly for 16 years, and others had been forming in the subcutaneous tissue above both elbows for approximately 10 years (figure 4). The tumor on his buttock had been injured and had developed an indolent, superficial, painful ulcer. The patient was hospitalized, and diagnostic study revealed no abnormality except a moderately enlarged prostate gland, evidence of mild cystitis, and the xanthomatous tumors. An oral glucose tolerance test showed an abnormal response, compatible with the diagnosis of diabetes mellitus. A serum cholesterol determination by the method of Abell et al.<sup>16</sup> was 240 mg.%. Because the tumor on the patient's buttock was so large (figure 5).

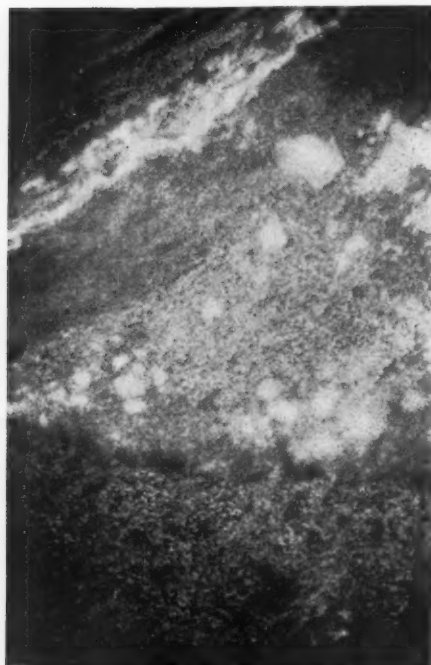


FIG. 3. A fresh, frozen section of the same area observed by ultraviolet microscopy. The large bright areas exhibit the fluorescence of carotenoid pigments. The linear streaks in the upper left corner are frayed elastic tissue.

it was considered to be a neurofibroma until it was removed and histologic examination revealed it to be a xanthoma. After the surgical wound on his buttock had healed, the patient requested removal of the tumors on his elbows, and agreed to have this done in two stages.

Serum carotenoids were determined prior to removal of the four largest tumors from his left elbow. Next he was given a supplementary feeding

TABLE 2  
Serum Carotenoids before and after Supplementary Beta Carotene Feeding

Date	Fraction I, $\mu\text{E. \%}$	Fractions II and III, $\mu\text{E. \%}$	Total Carotenoids, $\mu\text{E. \%}$
12-21-55	21	49	70
(Supplement started)			
1-24-56	56	44	100
2-1-56	133	61	194
2-6-56	204	70	274
2-16-56	362	105	467
2-23-56	264	74	338
(Supplement stopped)			
2-29-56	81	41	122

of carotenoids (17 mg. per day of a mixture of alpha and beta carotene in 10 c.c. corn oil\*). His diet was not restricted or measured. Total serum carotenoid levels were measured weekly for seven weeks and were fractionated on alumina.<sup>7</sup> Table 2 shows these determinations. An impressive increase in fraction I carotenoids (predominantly beta carotene) is shown. After five weeks, the four tumors from the right elbow were removed and the carotene supplement was stopped. The tumors removed before and after carotene feeding are shown in figure 6. These tumors



FIG. 4. The back and elbows of a 77 year old Negro male with mild diabetes mellitus. Massive xanthomas are seen on both elbows.

were weighed separately, and the fraction I carotenoid content (beta carotene) of each was determined by chromatography on alumina. The results are shown in table 3, which demonstrates that a significant increase in fraction I carotenoids occurred in three of the tumors removed after carotene feeding. These tumors, the smallest of their group, showed a fraction I carotenoid content double that of tumors removed before carotene feeding. On gross examination these tumors were visibly more yellow

\* Barnett Laboratories, Inc., 6256 Cherry Avenue, Long Beach 5, California. Approximately 90% beta carotene.



FIG. 5. A xanthoma, 8 cm. across, which was removed from one buttock of the patient shown in Fig. 4.

than the others, and were diffusely stained with pigment. Unfortunately, this experiment was performed before it was known that carotenoids can be visualized by ultraviolet microscopy, and so the exact microscopic deposition of pigment is not known. However, the experiment clearly indicates that infiltration of carotenoids occurred in three of the tumors. If we assume that these tumors originally contained the same concentration



FIG. 6. The elbow xanthomas removed before and after carotene feeding. Those on the left were removed before carotene feeding.



of carotenoids as the tumors removed before carotene feeding, it can be calculated that each was infiltrated by approximately 40  $\mu$ g. of carotene.

These studies of carotenoids in atheromas and xanthomas furnish information of value in understanding the manner in which atheromas grow. An outstanding feature of atheromatous growth is the accumulation of lipid. The source of this lipid, which is chiefly cholesterol, phospholipid and neutral fat, is controversial. One view is that blood-borne lipids infiltrate the arterial wall to form atherosclerotic plaques. This view receives support from an experiment in which tritium-labeled cholesterol was fed to man and later recovered from the aorta.<sup>17</sup> Opposed to the theory of lipid infiltration is a second view, which holds that atheromatous lipid is generated within the arterial wall by synthesis. This possibility is made

TABLE 3  
Carotene and Cholesterol Content of Xanthomas Removed before and after Carotene Feeding

Tumor	Wet Weight (gm.)	Dry Weight (gm.)	Fraction I carotenoids ( $\mu$ g./gm.)	Cholesterol (mg./gm.)	Carotenoids/ $\mu$ g. Cholesterol/mg.
Tumors removed before carotene feeding (1-10-56)					
1	8	2.4	16.9	187	.091
2	21	6.7	17.6	216	.082
3	14	4.2	18.5	216	.085
4	33	11.2	17.6	226	.086
Tumors removed after carotene feeding (2-20-56)					
5	24	7.3	17.9	195	.092
6	18	5.3	17.0	184	.092
7	18	5.4	12.9	145	.090
8	9	2.5	33.9	207	.161
9	8	2.4	31.5	240	.131
10	13	4.1	27.5	227	.121

credible by the finding that blood vessels contain the necessary ingredients for enzymatic synthesis of cholesterol and phospholipid, and that synthesis of these substances can occur *in vitro* when arteries are removed from the body. Because of these conflicting lines of evidence as to what human arteries can do, the question of lipid accumulation in growing atheromata must be stated as follows: What accounts for the lipid in atheromas as they grow in man under the usual circumstances of life: lipid synthesis or lipid infiltration? There is evidence that both *can* occur. Which *does* occur? These studies of carotenoid pigments indicate that a usual occurrence as atheromas grow is the infiltration of a lipid which can originate only in diet. Almost any autopsy provides evidence that carotenoids occur in early atheromas. In 30 unselected patients, atheromas of all ages demonstrate that carotenoids accumulate as rapidly as does cholesterol, the major

lipid present. In 20 other unselected patients, fluorescence microscopy indicates, by a second technic, that carotenoids are scattered at random through the lipid-bearing parts of the atheroma. It therefore seems clear that at least part of the growth of atheromas is due to the infiltration of an exogenous lipid.

These findings do not indicate that lipid infiltration is the sole means by which atheromas grow; although they furnish clear-cut evidence of lipid infiltration, they do not negate the possibility of concurrent lipid synthesis. It should be noted that carotenoids are a minor constituent of atheromatous lipid, and that a major portion of this lipid remains unaccounted for. However, if synthesis *in situ* occurs, it does so in such manner that the lipid synthesized is always available for infiltration by carotenoid pigments. It seems unlikely that the arterial wall synthesizes all of the lipid in the atheroma except carotenoids, and makes this lipid accessible for infiltration by carotenoids, meanwhile excluding all other exogenous lipid. A more likely possibility is that a significant contribution to the lipid of atheromas is made by the infiltration of serum lipids.

An initial approach to the rate and manner of lipid infiltration into atheromas is available through study of xanthomatous tumors. The microscopic anatomy of xanthomas is strikingly similar in many respects to that of atheromas,<sup>20</sup> although xanthomas are somewhat more vascular. The experiment reported here gives evidence that xanthomas can be influenced by exogenous lipid in a period as short as five weeks. Microscopic details of this process are not available, but a repeat experiment employing fluorescence microscopy to relate the deposition of carotenoids to the blood supply of these tumors should be informative. Also, it would be of great interest to learn if all xanthomas, or only certain of them, will accept carotenoids. The evidence so far suggests that small xanthomas are more readily affected than are large ones.

One other aspect of carotenoid pigments and atherosclerosis is worthy of mention. This is the intricate manner in which diet, environment and the metabolic state of man interact to influence the carotenoid content of atheromatous lesions. If man ingests an unlimited variety of carotenoids, all of them appear in atheromas. If racial or cultural factors affect the selection of carotenoids in diet, this is reflected in the pigment composition of atheromas. A high-fat diet favors the absorption of carotenoids; however, none can be absorbed from a carotenoid-free diet, regardless of fat content. Although carotenoids are ultimately derived from plant sources, the composition of human diet can be affected by intermediate carotenoid hosts. (Probably the most important of these in the American diet is the chicken; carotenoids are extracted from grain and concentrated in egg yolk.) All of these factors are modified by the intestinal function and metabolic state of the individual. Persons with intestinal malfunction extract few pigments from diet. Diabetes favors the accumulation of carote-

noids; thyrotoxicosis discourages it. In addition, genetic factors affect blood carotenoid levels, as do unknown factors which occur during acute infection. Thus, many variables determine the behavior of carotenoids in man and affect the color of human atheromas.

#### SUMMARIO IN INTERLINGUA

Pigmentos carotenoidic es lipidos colorate. Illos non es synthetisate per tissus human. Le nivello de carotena in sanguine e tissus human pote esser elevate o abassate per alterar le ingestion de carotenoides in le dieta. Specific lipoproteinas transporta le carotenoides in le sanguine. Le color jalne de xanthomas e atheromas es le effecto de pigmentos carotenoidic. In atherosclerotic aortas human le contento de carotenoide cresce constantemente con le augmento del dimensiones e del grado de severitate del atheromas. Microscopia fluorescential indica que carotenoides es seminate al hasardo in omne partes del lesiones atherosclerotic.

Un opportunitate de studiar le infiltration de carotenoides in anormal massas lipidic esseva offerite per un masculo de 77 annos de etate qui habeva diabete e grande xanthomas in ambe cubitos. Quatro xanthomas esseva removite ab le cubito sinistre. Postea le nivellos sanguinee de carotena esseva augmentate per le administration de carotena beta per via oral. Cinque septimanas plus tarde, sex xanthomas esseva removite ab le cubito dextere. Il esseva constatate que le tres plus grande inter le sex xanthomas non habeva augmentate lor contento de carotena. In le tres plus micre xanthomas le contento de carotena beta esseva reduplicate.

Iste constatationes indica que anormal massas lipidic in xanthomas pote esser influentiate per lipidos dietari. Le presentia de carotenoides in atheromas human indica que lipido exogene infiltra in iste lesiones.

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## FURTHER OBSERVATIONS ON LICHEN MYXEDEMATOSUS \*

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WHETHER referred to as lichen myxedematosus, papular mucinosis, or lichen fibromucinoidosis, the clinical circumstance of mucin deposited in the skin in the form of papules, nodules or plaques is now generally accepted as the cutaneous expression of the same pathophysiologic process. This group of terms, however, is distinct from the earlier choices, "generalized localized myxedema" and "scleromyxedema."

The earlier reports of Dalton and Seidell<sup>1</sup> and of Montgomery and Underwood<sup>2</sup> have clarified the essential features of the disease, so that numerous reports of it can now be found in the literature. In addition to those included in the paper by Zakon and Johnson,<sup>3</sup> a few other cases have been reported recently in the United States.<sup>4,5</sup> Cases of lichen myxedematosus have been reported in Germany,<sup>6-8</sup> France,<sup>9-13</sup> England<sup>14,15</sup> and elsewhere.<sup>16,17</sup> Bibliographic references have been offered by Von Zezschwitz<sup>8</sup> and by De Graciansky and associates.<sup>11</sup> The number of reports seems to indicate that the incidence of the disease is increasing, but this may reflect only mounting diagnostic acumen and clinical appreciation of the entity.

### CLASSIFICATION

The schema devised by Montgomery and Underwood<sup>2</sup> for classification of the cutaneous myxedematous (mucoid) states remains, with slight revision (table 1), an acceptable framework for the presentation of our clinical experience with the problem of lichen myxedematosus. It is easy to distinguish generalized myxedema, in which cutaneous changes are associated with true hypothyroidism, from localized pretibial myxedema (circumscribed or localized solid edema), in which the skin lesions are almost—but not quite—always associated with thyrotoxicosis, and to distinguish both from the third entity, lichen myxedematosus.

The various forms of lichen myxedematosus are plainly differentiated from one another by their morphologic characteristics. That listed first—the generalized lichenoid form of the disease—appears as discrete papules,

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uniform in size, usually 2 to 3 mm. in diameter, which are distributed generally over the entire body but seem to have a predilection for the hands, forearms, upper part of the trunk, face and neck. At times, close scrutiny is required to find these flesh-colored lesions (figure 1). Associated with the individual papules is a peculiar firm induration of the underlying tissue, producing a resemblance to scleroderma both on visual inspection and on palpation.

Authors have commented on the manner in which the furrows of the brow are thrown into large folds, giving the patients a saddened look (figure 2). The induration of the tissues becomes such that facial expressiveness



FIG. 1. Generalized lichenoid variety of lichen myxedematosus. Grouped lichenoid papules, discrete and of uniform size, are distributed generally over the body.

is restricted and movement of the jaws impaired. It is this characteristic which produces confusion in the differential diagnosis of scleroderma. The papular lesions may eventually become generalized, and the induration such a problem that movement of the extremities, including walking, is difficult.

The second form of lichen myxedematosus includes the discrete papular forms (figure 3), in which flesh-colored to red, variously sized papules are present over the trunk and extremities. The lesions in such cases are not nearly so numerous as in the generalized lichenoid variety, being perhaps fewer than 50. Such lesions might be confused with sarcoid, keloid or the tumor formations of syringoma.

Perhaps a subclass of this second form is the annular lesions, which have been described as similar to "candy lifesavers" inserted into the skin (figure 4). These lesions present an elevated, rounded, indurated margin, brownish-



red or possibly flesh-colored. Within the margin is a depressed area of atrophy with hypopigmentation and scaling, sometimes having keratogenic scaling at the center. It is this type of lesion that Caro<sup>18</sup> emphasized might represent a distinct subdivision within the larger group of lichen myxedematosus, because the indurated, ring-like lesions differ so much morphologically from the usual papules of lichen myxedematosus.

The third form of lichen myxedematosus is manifested as localized to



FIG. 2. Generalized lichenoid variety of lichen myxedematosus. Group lesions are accompanied by induration of underlying tissue, which at times assumes an undulated, rugate configuration. Occurrence on the face gives the patient a despondent expression.

generalized lichenoid plaques which, for the most part, resemble patches of generalized lichen planus. Lichenoid papules can be seen interspersed over the body, but generally the individual lesions have fused to form lichenoid plaques.

The fourth form appears initially as urticarial plaques and nodular eruptions, but frequently the lesions change into other forms of lichen myxedematosus. Authors have described cases where this initially urticarial variety turned into the generalized lichenoid form. Possibly this fourth form and the third might best be combined as a single lichenoid variety.

The exact classification of the plaquelike form of cutaneous mucinosis (recently described by us)<sup>19</sup> is difficult, inasmuch as the individual lesions composing the plaques are urticarial and not lichenoid papules. Since the fourth form of lichen myxedematosus begins as urticarial lesions, and the plaquelike form of cutaneous mucinosis presents an urticarial quality, this latter type may best be classified under that same heading.

#### HISTOPATHOLOGY

The histologic features revealed by skin biopsy in lichen myxedematosus are considered to be characteristic, although difficulty is encountered in

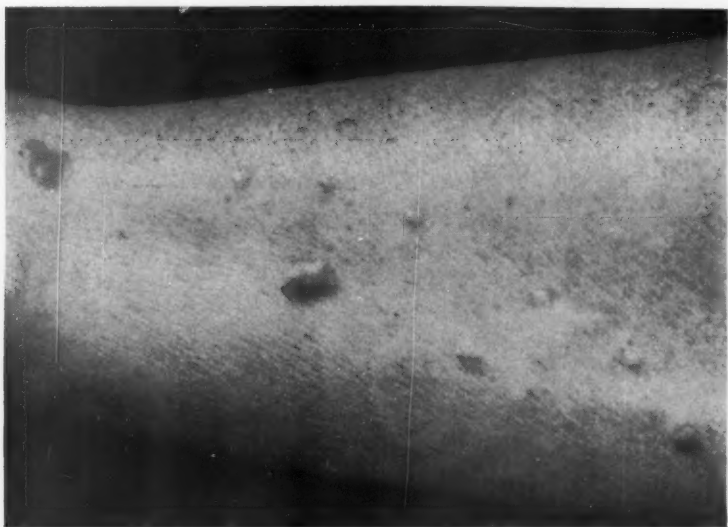


FIG. 3. Discrete papular form of lichen myxedematosus. The relatively few papules and nodules vary in size, but retain their discreteness.

distinguishing this entity from other forms of myxedema, particularly localized pretibial myxedema. Frequently, however, the latter disease presents considerably more hyperkeratosis than does lichen myxedematosus, in which the thickness of the keratin layer is normal or only slightly increased.

*Alterations:* Epidermal changes are usually minimal. Probably because of pressure from the mucinous deposits beneath the epidermis, the epidermis may be thinned, with flattening of the rete ridges and obliteration of the papillary bodies. The cells of the malpighian and basal layers may show varying degrees of pyknosis.

The diagnostic alterations of the skin in mucoid states are seen within the cutis, especially in the upper portion. Because of the marked edematous

quality of the involved areas, the collagen bundles appear to have been split and fragmented into a loose fibrillar network, and this same loose arrangement of the collagen tissues is also noted about the hair follicles and other



FIG. 4. *Case 2.* Probable subclass of papular form of lichen myxedematosus. Annular lesions with central atrophy, depression and atrophic scaling.

skin appendages. A fine granular material is present about some of the fibrils (figure 5).

Interspersed irregularly throughout the affected area are the large stellate cells, resembling fibroblasts, which are the predominant histologic fea-

ture. At times the fibrils appear to be contiguous with them, thus seeming to originate from them.

In the older lesions, the fibroblasts become more numerous and fibrosis is increased. This feature accounts for the term "lichen fibromucinoidosis," employed by Lorincz.<sup>5</sup>

Various amounts of cellular infiltrate (chiefly lymphocytic) may be noted about the blood vessels and skin appendages. Mast cells may or may not be present in it, but never to the extent seen in urticaria pigmentosa. Histiocytes and polymorphonuclear cells may be mixed in the infiltrate. The stellate cells are not necessarily found in association with the inflammatory

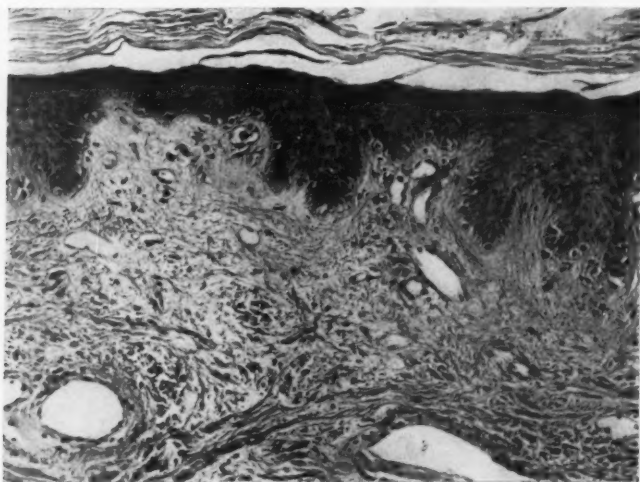


FIG. 5. *Case 1.* Material from skin biopsy. Upper corium contains loose fibrillar network of frayed and fragmented collagen fibers, together with fine granular material, both of which stain positively for mucin. Large stellate cells, probably fibroblasts, and numerous dilated capillaries are also interspersed within this area (hematoxylin and eosin;  $\times 25$ ).

infiltrate, although they may be found in this location also. Bazex and Dupré<sup>12</sup> have maintained that the fibroblast is the cellular element necessary for diagnosis, and that other abnormal cellular elements are absent, a finding with which we are in disagreement.

*Analysis by Staining:* In this disease the mucinous deposits usually stain bluish-red with hematoxylin and eosin, and special stains clarify the changes further. With Mayer's mucicarmine stain the mucinous deposits stain a bright red, in contrast to the pink of normal collagen. Under these circumstances, it can better be ascertained that the fibril strands of mucin are connected with the previously described stellate cells that are distributed throughout the edematous area. The granular material surrounding these cells also stains red with the mucicarmine stain. Toluidine blue staining of

sections in lichen myxedematosus reveals this material to be metachromatic, taking a light purple color, in contrast to the blue of the other tissues.

Staining of sections with methyl violet reveals no alteration that suggests the presence of amyloid. Congo-red staining also is negative for amyloid.

As reported in the literature, our own experience confirms the observation that diastase treatment of sections does not alter the material. However, treatment of a section with hyaluronidase prior to counterstaining with toluidine blue removes this mucinous material from the slide, because the metachromasia disappears on sections so treated. Johnson and co-workers,<sup>20</sup> reporting on alopecia mucinosa, compared the lesions of this disease with those of localized myxedema, generalized myxedema and papular mucinosis. It was their impression that the mucin in all of these entities was similar because it showed the same qualitative histologic changes.

Cawley and associates<sup>21</sup> studied normal skin and skin from a patient with lichen myxedematosus by means of the Mowry's alcian blue-periodic acid-Schiff technic, and found the mucinous materials to be composed of acid mucopolysaccharides.

Beierwaltes and Bollet<sup>22</sup> studied the mucopolysaccharide content of skin from patients with pretibial myxedema by means of chemical analysis, using the carbazol and orcinol methods of determination, and found that the acid mucopolysaccharides were increased in these lesions approximately tenfold, whereas uninvolved skin showed only a twofold increase in acid mucopolysaccharides. Lorincz and Lynfield,<sup>5</sup> in discussing a case of lichen fibromucinoidosis presented before the Chicago Dermatological Society, reported that analyses of tissue in that one case showed that tissue content of acid mucopolysaccharide was increased, although the urinary excretion of polysaccharides was not increased.

### ETIOLOGY

The etiology of lichen myxedematosus remains obscure. Although this disease has been characterized by normal endocrine function to date, occasional articles still raise the question of disturbance in thyroid function. In patients we have studied, normal thyroid function has been the rule.

Curtis and his associates<sup>23</sup> emphasized the influence of the thyrotropic hormone of the anterior pituitary in the pathogenesis of malignant exophthalmos and localized pretibial myxedema. When no definite thyroid endocrinopathy can be proved in lichen myxedematosus, it is difficult to explain the deposits of mucin which are so similar by the histopathologic and histochemical technics now available.

Gottron,<sup>24</sup> in 1954, speculated on the possible formation of mucin from collagen fibers. More recently, Cawley and associates,<sup>21</sup> in studying cutaneous mucinosis by Mowry's alcian blue-periodic acid-Schiff technic, thought that merging of some threads and strands of mucin with the col-

lagen fibers and fibrils could be demonstrated. In the discussion of their report, Cawley emphasized the belief set forth in it—that mucin in cutaneous mucinosis may be derived from the collagen—although proof of this is lacking.

Tappeiner<sup>25</sup> considered lichen myxedematosus to be a constitutional disease caused by liver damage, which results in the formation of mucoid substances that are deposited in the skin. In patients whom we have studied recently, we have found no clinical evidence of liver disease. On the basis of Tappeiner's hypothesis of disturbed liver function, specific liver function tests have been carried out, and their results, too, have been reported as normal.

The fact that hyaluronidase will clear a slide of the mucinous material suggests that alteration of hyaluronic-acid metabolism may be involved in the production of the cutaneous mucinosis. Anderson has speculated on this thesis in his comments on the paper by Cawley and associates.<sup>21</sup>

The possibility that patients with lichen myxedematosus have an associated systemic disease is to be considered.

#### CASE REPORT

In the recent past we have had an opportunity to study a patient who presented with the generalized lichenoid variety of lichen myxedematosus in association with multiple myeloma. We wish to emphasize here that the lesions seen in this patient were those of lichen myxedematosus, and not a part of the usual cutaneous manifestations of multiple myeloma described by Bluefarb.<sup>26</sup> A summary of our findings follows.

*Case 1.* A 53 year old man seen at the Mayo Clinic in October, 1957, complained of a skin eruption which had been present some six years. The process had begun on the arms, but within a two-year period had become generalized. The initial lesion had been a small, erythematous papule; subsequently, annular lesions and plaques had developed over the body. Pruritus definitely had been present, some lesions causing discomfort and pain. The patient had no systemic complaints. He was able to carry on with his work as a grocer, although it was difficult for him to bend his legs because of induration of the skin.

Previous therapy had consisted of administration of prednisone through a six-month period, three injections of nitrogen mustard given in a two-week period, and courses of quinacrine (Atabrine) and thyroid. Superficial x-ray therapy had been administered to the arms, abdomen and back over a six-month period during 1951, and had been repeated in 1953. It was the patient's impression that no benefit had resulted from any of these treatments.

Examination of the skin revealed that the disease involved the entire body, with sparing of the face and neck, the flexures of the arms and legs, and the soles of the feet. The individual lesions were annular and gyrate, somewhat urticarial plaques of various sizes scattered over the body. Centrally, these lesions showed an area of atrophy, with telangiectasia coursing over it and the adjacent tissues. The tissues of the legs were sufficiently thickened that bending of these members was difficult.

A general examination disclosed no other abnormal physical findings. There was no unusual lymphadenopathy, no splenomegaly, and no evidence of purpura.



Laboratory examinations gave normal or negative results in respect to hemoglobin, erythrocytes, leukocytes, a serologic test for syphilis, and a lupus erythematosus clot test. Urinalysis showed albumin as 1 to 2 plus, occasional hyaline and granular casts, and 1 plus erythrocytes. A chest x-ray showed torsion of the aorta but was otherwise within normal limits. In the serum, protein measured 7.65 gm. per 100 ml.; albumin, 3.95 gm.; globulin, 3.7 gm.

Electrophoresis of serum protein, done because of the abnormal albumin/globulin ratio, gave the following results: albumin, 2.88 gm. per 100 ml.; alpha 1 globulin, 0.44 gm.; alpha 2 globulin, 0.86 gm.; and beta globulin and gamma globulin, 3.02 gm. It was noted that this serum gave a high, sharp bank over the  $\beta$ -region and extended over the forepart of the gamma.

Further studies on the serum were undertaken by Dr. David Evenson.<sup>27</sup> These studies on the carbohydrate content of the abnormal protein showed it to be quite

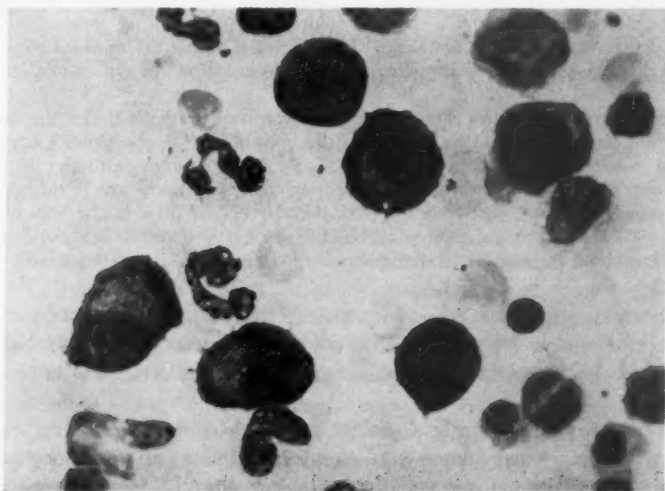


FIG. 6. Smear of bone-marrow aspirate showing plasma myeloma cells (Wright's stain;  $\times 1000$ ).

different in make-up from the classic "M" protein of the multiple myeloma group. (A similar situation has been found in only two other cases, one of primary systematized amyloidosis, and one of portal cirrhosis.)

Examination of marrow showed hypercellularity with a background of rouleau formation, with all marrow elements represented. Average myelopoiesis was present, but with a shift to the left. The erythropoiesis was not remarkable. Scattered throughout the normal elements were a considerable number of mature and moderately immature plasma cells and small focal aggregates of lymphocytes. The diagnosis was multiple myeloma (figure 6).

A roentgenographic survey that included the lumbar vertebrae, the right femur and the head gave no evidence of bony destruction. However, small deposits of calcium were found in extensive, widely distributed areas of the subcutaneous soft tissues of both thighs, the flanks and the groin. An electrocardiogram was interpreted as being normal. Special measures to rule out thyroid dysfunction included determination of the basal metabolic rate as plus 4, and the protein-bound iodine as 4.5 mg. per 100 ml. of serum.

Biopsies of the skin lesions on the upper back, the right scapular area and the left forearm gave similar findings, except that the changes in the lesion on the left forearm were less marked than in the other two. The epidermis was normal, without appreciable thinning or obliteration of the rete pegs. In the upper corium, and extending well into each of the papillary bodies, was an areolar network of fine fibrous strands, some of which seemed to be attached to large stellate cells that were scattered sparsely within this area. A fine granular material was enmeshed within the network, and on microscopic sections this material, as well as the fibrous stroma, stained somewhat bluish with hematoxylin and eosin. This same areolar lacework of fine strands was seen about the hair follicles and the vessels of the upper corium, accompanied by an infiltrate which was primarily lymphocytic and was free of the large stellate cells seen in the upper corium.

These fibrils and the granular material stained positively with mucicarmine and metachromatically with toluidine blue, but negatively for mucopolysaccharides with the periodic acid-Schiff technic. Hyaluronidase digestion of an unstained section eradicated this material from the slide. Methyl violet stains for amyloid were negative, and diastase digestion of the slide revealed no essential change from the control slides.

After dismissal from the clinic, the patient received urethane under the direction of his home physician, but this had to be discontinued after six months because of persistent nausea and vomiting. Despite this period of therapy with the drug there was no appreciable change in his skin lesions, nor was there amelioration of the marked pruritus. Since that time the patient has received little in the way of active therapy. An answer to an inquiry as recently as a few months ago indicated that his skin was about the same, and that generally his disease had not progressed.

*Comment:* As far as we know, this is the first reported occurrence of multiple myeloma in a patient with a cutaneous mucinosis, and probably the two should be considered to be coincidentally rather than etiologically related.

The opportunity to study a patient with lichen myxedematosus in association with multiple myeloma was of interest, inasmuch as among patients with multiple myeloma we usually encounter the cutaneous deposition of amyloid rather than of mucin. The histopathologic reactions evidenced in the skin biopsies were those of lichen myxedematosus, methyl violet staining of tissue sections being negative. Hence we believe that the cutaneous pattern was that of papular mucinosis rather than of cutaneous amyloidosis. Because the exact chemical natures of mucins and amyloid remain unknown, this chance association might lead to some conjecture on the relative origin of these substances in patients with multiple myeloma.

#### DIFFERENTIAL DIAGNOSIS

The differential diagnosis of lichen myxedematosus includes a variety of clinical conditions. A nodular form of scleroderma may be considered first, because of the presence of the numerous small papules and associated induration of the skin—particularly of the face, neck, upper part of the trunk, hands and forearms—mentioned as characteristic of the generalized lichenoid papular form of lichen myxedematosus. It is this condition which previ-

ously had been reported as scleromyxedema. Skin biopsy of a large number of patients with various forms of scleroderma, however, has not revealed mucin in those specimens as it has in skin affected by lichen myxedematosus.<sup>28</sup>

When lichenoid papules are generalized over the body they must be differentiated from lichen planus, lichen nitidus and pityriasis rubra pilaris. Because at times the papular element is less distinct and the induration of the tissues is more pronounced, the possibility of pseudoxanthoma elasticum or lichen ruber moniliformis must be considered. Mucin apparently is not present in the latter condition.

More localized forms of lichen myxedematosus require differentiation: urticaria pigmentosa, sarcoid, granuloma annulare, epithelioma adenoides cysticum, and syringoma. These various entities differ, however, in their individual characteristic histologic appearances, and so can be distinguished under the microscope.

#### TREATMENT

No specific therapy for lichen myxedematosus is available. In the past, treatment with thyroid has failed.

Dalton and Seidell<sup>1</sup> initially reported the disappearance of such lesions with the local injection of hyaluronidase, followed by subsequent pressure on the affected site. Contradictory evidence was presented by Chivington,<sup>29</sup> who reported that after injection of hyaluronidase into a single lesion of lichen myxedematosus, he was unable to ascertain any appreciable change in the skin lesions.

In the case here reported, with multiple myeloma, treatment of the multiple myeloma exerted no influence upon the cutaneous lesions.

In a previous publication,<sup>19</sup> our experience using quinacrine in lichen myxedematosus is mentioned. Further observations on such cases will be necessary before the therapeutic value of such treatment is verified.

The foreign literature has indicated that the use of Lipiodol<sup>13</sup> and thyroid<sup>10</sup> or x-ray<sup>15</sup> therapy is of value; but Lorincz and Lynfield<sup>5</sup> recently reported the employment of a variety of local and systemic treatments in a patient with lichen myxedematosus, without benefit to the patient.

The efficacy of steroids in the treatment of patients with lichen myxedematosus remains to be evaluated. Donald and co-workers<sup>16</sup> reported that alternating courses of ACTH and cortisone failed to benefit their patients.

Dalton<sup>30</sup> has advised us that he and his co-workers will soon publish their experience with the use of steroid preparations in two cases of lichen myxedematosus.

#### NECROPSY FINDINGS

McCuiston and Schoch<sup>31</sup> reported the necropsy findings in the case of a patient with lichen myxedematosus who had been seen during life by

numerous clinicians. The diagnosis was confirmed histologically by various examiners. Postmortem studies revealed that the mucinous material, in addition to being found in the skin, was found also in the connective tissue about the blood vessels of many organs, including the heart, kidney, pancreas and adrenal glands. Even so, there was no apparent cause for the death of this patient.

Donald et al.<sup>16</sup> report on their necropsy findings in the case of a 51 year old man who had the generalized papular form of lichen myxedematosus. His death followed a period of treatment employing ACTH and the adrenal steroid hormones. The histologic evidence of mucinosis in this patient was scant. The only positive finding was that of a nodule of large cells containing neutrophilic granules in the pars nervosa of the pituitary gland. The final impression of the investigators, however, was that these were ordinary neutrophilic cells in an unusual site.

Montgomery and Underwood<sup>2</sup> in their original paper reported the clinical findings in a 56 year old woman who had a generalized papular form of lichen myxedematosus. Her course was followed in her home community by dermatologist colleagues in that area.\* This patient gradually became debilitated and emaciated, and finally was hospitalized early in 1953, being disoriented and agitated and having fever. She died approximately one month later, at age 61 years, having had her disease for approximately six years. Necropsy was performed and permission for evaluation of this material was granted by the local pathologists.† The lungs showed bronchopneumonia, which was a part of her terminal illness. Congestion of the spleen was noted, as well as congestion of the adrenal medulla and depletion of the lipoids in the adrenal cortex. Deposition of mucin in the various body organs was not noted.

*Case 2.* A previously unreported case of lichen myxedematosus is that of a 36 year old man who was seen at the Mayo Clinic in 1954. He gave a history of skin lesions that had appeared first on his back some three years earlier (figure 4). The lesions gradually spread to the arms, chest and abdomen, and finally to the lower extremities. The lesions were asymptomatic except for pain produced by direct pressure on them. On examination they were seen to be discrete and annular, with a somewhat firm, indurated border. Centrally there was marked depression with atrophy, scarring and, in some, an amorphous keratogenous material.

At the time the patient came to the clinic he was complaining of intermittent periods of numbness of all extremities and of some incoördination of his legs. It was considered that his neurologic problem could best be explained by focal encephalopathy, but the neurologist hoped that all findings, including the dermal, could be explained by a single systemic syndrome.

Upon the patient's return to his home, clumsiness of the left leg developed, with a tendency to drag this member. Symptoms progressed so that two months later both legs were paralyzed, and he had no sensation below the level of the nipples.

\* Dr. Stephen Rothman and Dr. Allan L. Lorincz kindly supplied data on the clinical course of this patient's illness.

† Dr. C. C. Mason and Dr. Herman Josephy kindly supplied pathologic material for histologic review.

Respiratory embarrassment occurred because mucus collected in the upper respiratory tract, and he lapsed into coma and remained semicomatose until he died early in October, some six months after we had seen him. Necropsy was performed and tissues were kindly submitted for our evaluation.\*

The brain showed fibrous thickening of the meninges, with multiple old and new infarcts, chiefly distributed in the white matter. Infarcts in the region of the posterior column were noted also. A focus of chronic pyelonephritis was found in one kidney, with mucin-positive material in the interstices of the renal papillae. The pituitary gland showed no remarkable changes. The adrenal cortices were depleted of their lipid material. Sections from the lungs showed foci of acute bronchopneumonia and chronic peribronchial inflammation; mucin-positive material was found in the bronchial secretion and bronchial epithelium, glands and cartilage. Mucin was seen also in the ductal epithelium of the pancreas.

*Comment:* Thus it appears from the necropsy material available that few positive findings are recognized except for the deposition of mucin within certain organs, as well as in the skin itself. There have been no findings that indicate a uniformity of abnormal physiology leading to specific pathologic findings at the time of death.

#### SUMMARY

Lichen myxedematous, as a grouping among the cutaneous myxedematous states, encompasses a number of rare diseases whose patterns of deposition of mucin differentiate them into distinct clinical entities. A working classification is presented.

TABLE 1

Classification of Cutaneous Myxedematous (Mucoid) States†

*True myxedema:* cutaneous changes in association with true hypothyroidism.

*Localized solid edema* (circumscribed or pretibial myxedema): almost always associated with thyrotoxicosis.

*Lichen myxedematous* (papular mucinosis or lichen fibromucinoidosis): no endocrinopathy present.

Generalized lichenoid papular eruption.

Discrete papular forms.

Localized to generalized lichenoid plaques.

Urticarial plaques and nodular eruptions that usually end in the lichenoid form.

† Modified from Montgomery and Underwood.<sup>2</sup>

The histopathologic findings in lichen myxedematous are distinctive but not pathognomonic, as similar microscopic alterations occur in the mucoid states.

The etiology of lichen myxedematous remains obscure. To date, evidences of associated specific systemic disease are not associated with regularity, and appear to be coincidental in occurrence. A case associated with multiple myeloma is reported.

\* Dr. R. L. Looker, Department of Pathology, St. Francis Hospital, Wichita, Kansas, permitted review of necropsy material.

The findings in isolated necropsies have revealed the presence of mucin in various organs in some cases, but such findings have failed to elucidate the pathogenesis of lichen myxedematosus.

Therapy to date remains unsatisfactory.

#### SUMMARIO IN INTERLINGUA

Le depositos de mucina intra le pelle in casos de lichen myxedematose (mucinosi papular) pote manifestar un distincte configuration morphologic que servi a differentiar los ab le cutanee depositos de mucina incontrate in myxedema generalisate e in localisate myxedema pretibial. Le autores ha summarisate le currente opiniones relative al classification, histopathologia, etiologia, diagnose differential, tractamento, e constataiones necroptic in le patientes afficite de lichen myxedematose e ha correlationate los con lor proprie experientias. Es addite duo previeamente non reportate casos de lichen myxedematose, incluse un que esseva associate con myeloma multiple. Le constataiones necroptic in duo casos non revelava un causa systemic del eruption cutanee.

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## AN APPRAISAL OF CERTAIN TESTS FOR THE DETECTION OF HYPERTENSION OF UNILATERAL RENAL ORIGIN\*†

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UNILATERAL renal disease may give rise to a reversible form of severe arterial hypertension.<sup>1-5</sup> The prevalence of such lesions is unknown, and there is no reliable method for screening hypertensive patients for such correctable disease. A number of tests have been developed to aid in the solution of this problem, and the following report summarizes our experience with such tests.

### REVIEW OF THE TESTS

1. *Differential Renal Excretion of Urine and Its Sodium Concentration:* In 1956 Howard et al.<sup>4</sup> reported that a significant reduction in urine volume and its sodium concentration from one kidney as compared to that obtained simultaneously from the opposite side was highly prophetic of correctable hypertension of unilateral renal origin. The following year these authors<sup>5</sup> extended their earlier observations and suggested criteria for the performance and interpretation of this test. These criteria were used in interpreting the data for this report.

2. *Translumbar Renal Arteriography:* Poutasse, Humphries, McCormack and Corcoran<sup>6</sup> have shown that this procedure provides an objective method for demonstrating lesions of the renal arteries, the only way at present to recognize bilateral renal arterial lesions.

The technic of translumbar arteriography as proposed by Smith et al.<sup>7</sup> in 1952 was employed in the study of the patients here reported.

3. *Tetraethylammonium Chloride Test (TEAC):* In 1957 Brust and Ferris<sup>8</sup> reported that a TEAC test produced a pressor response or no appreciable fall of blood pressure in patients with renal vascular lesions, and a depressor response in patients with renal parenchymal disease (pyelonephritis).

4. *I<sup>131</sup>-Labeled Diodrast Renograms:* Winter<sup>9</sup> in 1957 proposed the use of radioactive Diodrast renograms as a screening test for unilateral renal

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disease. An appreciable delay, or diminution of the initial peak of the curve of gamma-ray emissions, was interpreted as impaired renal blood flow to that kidney. The technic employed in investigating the patients here reported was described in 1956.<sup>10</sup>

## RESULTS

1. *Differential Renal Excretion of Urine and Its Sodium Concentration:* Simultaneous measurements of urine volume and its sodium concentration by means of bilateral ureteral catheters were performed on 122 patients. With the use of the criteria suggested by Howard and his co-authors,<sup>8</sup> the test was satisfactory in 67 patients (55%) and unsatisfactory in 55 (45%).

A. *Satisfactory Tests.* Among the 67 patients with satisfactory tests were three whose tests revealed a reduction of urine volume of 60% or more, and a reduction in sodium concentration of 15% or more on the same side (positive test).

## CASE REPORTS

*Case 1.* A 51 year old man was hospitalized because of minimal active pulmonary tuberculosis. Asymptomatic hypertension had been present for at least 15 years, but there was no evidence of any recent change. Hypertensive cardiovascular disease was common in his family. Examination on admission disclosed Keith-Wagener Grade 2 retinopathy, and his blood pressure ranged between 220/95 and 240/108 mm. Hg. Serial urinalyses gave reactions ranging from alkaline to acid, maximal specific gravity of 1.018, and 0 to 2 plus albuminuria. The hemogram and blood chemical studies were normal. Chest x-ray revealed patchy infiltration in the left upper lobe and a normal-sized heart. An excretory urogram was normal except for a 1.5 cm. area of calcification, with a sharply delineated peripheral rim, thought to represent an aneurysm of the left renal artery. Differential renal excretory studies are shown in table 1. The patient refused additional diagnostic studies. There has been no change in his hypertensive disease in the four years since these observations were made.

*Case 2.* A 51 year old man was first hospitalized because of a bleeding gastric ulcer. He was not aware of elevated blood pressure, and there was no history of hypertension in his family. On examination he was found to have Keith-Wagener Grade 3 retinopathy, and blood pressure of 190/120 mm. Hg in each arm. When the acute illness had stabilized, laboratory investigation of his hypertension showed persistent albuminuria, ranging from a trace to 3 plus, maximal specific gravity of 1.014, granular casts, and microscopic pyuria and hematuria. The urea nitrogen was initially 39 mg.%, and fell to 23 mg.%. Electrocardiograms disclosed changes consistent with anterolateral myocardial damage and probably left ventricular hypertrophy. X-ray examination of his heart was normal. An excretory urogram disclosed delayed appearance time of the dye bilaterally, particularly on the left. A TEAC test gave a pressor response. Differential renal excretory functions were abnormal, showing significant reduction in sodium concentration and urine volume in the first collection period, and questionable results in the second period (table 1). The patient was discharged on an ulcer regimen to be followed in the Outpatient Department.

The patient was re-admitted six weeks later, at which time Keith-Wagener Grade 4 retinopathy was present, and his blood pressure averaged 230/140 mm. Hg. A

TABLE 1—Comparison of Results of Four Tests for Detection of Unilateral Renal Hypertension

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (ml) and Sodium Concentration (mEq./L.)			Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	I <sup>131</sup> -Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder				
1		18 — 103	67 — 133	2 — ?				Excretory urogram was suggestive of aneurysm, left renal artery
2	9/25/58	11 — 85	33 — 106	2.5 — ?		Pressor response in initial test		There were advanced nephrosclerosis and moderate chronic pyelonephritis bilaterally at autopsy. The main renal arteries were patent
		11 — 97	33 — 102	0.3 — ?				
	11/6/58	19 — 37	11.8 — 36	0.3 — ?	Bilateral impairment of intrarenal arteriole but normal renal arteries	Depressor response	Slightly decreased vascularity on right, marked on left	
		16 — 31	10.4 — 30	0.3 — ?				
		25 — 27	17 — 25	0.5 — ?				
3	6/28/58 (500 mg. Na diet)	42 — 24.5	7.5 — 12.6	0 — ?	Only 2 cm. of left renal artery visualized. Three fine vessels led to left kidney. Nephrographic effect, upper half			Blood pressure returned to normal following right ureteronecystostomy and sectioning of an obliterated congenital vessel obstructing the right ureter
	7/8/58 (500 mg. Na diet)	15.5 — 3.5	4.2 — 4.7	0.5 — ?				
		16 — 3.7	6.5 — 4.7	7.2 — 4.8			Pattern of obstructive uropathy on the right	
	10/2/58	39 — 173	30.5 — 214	1 — ?				
	1/14/60	25.8 — 144	13.2 — 216	0 — ?	Normal renal vascularization, bilaterally			

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (ml.) Sodium Concentration (mEq./L.)			Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	I <sup>131</sup> -Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder				
4		Upper† 15.2 Lower† 28 60	29 60.5	32 62.5	Narrowing of origin of aberrant artery to lower pole, left kidney	Depressor response	Both curves normal, but slightly more vascular on the right	At operation, both arteries entering left kidney were patent and pulsatile. Left nephrectomy did not alter her blood pressure.
		Upper 25 77 Lower 31 70	27 70	2.8 ?				
	5/1955	76 7.2	50 8	Not recorded.				
5	9/30/57	46 19	37 23	2 9	Marked narrowing of left renal artery with decreased vascularization		Pattern of ischemia on left	Three arteries supplied the left kidney. One supplying lower pole was thickened and its lumen was narrowed. Left nephrectomy did not alter her blood pressure.
		23 66.8	36 64	11 66.4				
	3/1958	30 16.6	35 15.6	6 18.8				
6		38 13.8	37 14.4	7 14.6	There was no vascular pattern in lower one third, right kidney, and nephrographic effect was absent	Pressor response (preoperatively and postoperatively)		Aberrant artery supplying lower pole of right kidney was occluded by a thrombus. Her blood pressure returned to normal after right heminephrectomy.
	8/21/58	23 3.1	20 2.9	0				
		21 2.5	27 2.4	0				

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

† Double collecting system, right kidney.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions*			Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	I <sup>131</sup> -Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder				
7		0 ?	62 73	0	Narrowing midportion of right renal artery†			Blood pressure returned to normal following right nephrectomy. ("Nonfunctioning" right kidney)
8		0.7 4	77 42.5	10 23.5	Narrowing of right renal artery 1 cm. from aorta with poststenotic dilatation containing a thrombus	Depressor response	Ischemic pattern on right side	Blood pressure returned to normal following right nephrectomy. ("Nonfunctioning" right kidney)
9		0.5 ?	70 41.5	15 40	One branch of right renal artery occluded and arteriole was diminished‡			His blood pressure returned to normal following right sympathectomy, adrenalectomy and nephrectomy
10		4 27.5	10 17	Not recorded				Systolic hypertension only. Right nephrectomy for hydronephrosis and multiple calculi caused slight lowering of her systolic hypertension and relief of her symptoms
11		8 22	15 30	Not recorded	Unsuccessful			At autopsy a recent thrombus was found in the renal artery, and the right kidney was severely affected by chronic pyelonephritis
12		50 50	48 61	2 ?	Normal renal arterial arteriole			His blood pressure returned to normal after sympathectomy for essential hypertension (?). The renal arteries were normal

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

† Patient developed pleural effusion.

‡ Possible complication of angiography. Neurologic emergency progressed to permanent paraplegia.

|| Complication of angiography. An intercostal artery was severed, with the development of large left hemothorax, resulting in death.



TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (ml.) Sodium Concentration (mEq./L.)			Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	<sup>131</sup> I-Labeled Diodrast Renogram	Remarks	
		Right	Left	Bladder					
13	11/25/59	38 — 6	18 — 11	1 — ?	Normal renal arterial arborization		Decreased vascularity, more marked on the left	At autopsy the renal arteries were patent. Chronic pyelonephritis was present in each kidney, and there were bilateral renal calculi	
		40 — 7	19 — 10	2 — ?					
		70 — 8.7	25 — 19.2	11 — 7					
	11/26/59	29 — 23.8	20 — 26.4	56 — 11.6					
		82 — 7	47 — 16	12 — 21					
14	8/8/56	19 — 16	41 — 21	2.5 — 9	Normal renal arterial arborization†			Contracted right kidney of undetermined etiology	
		36 — 50	30 — 51	11 — 42					
		38 — 42	38 — 46	21 — 42					
	7/19/57								Ischemic pattern bilaterally, more marked on the right

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

† Complication of angiography. Patient developed pleural effusion.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (mL) Sodium Concentration (mEq./L.)			Translumbar Renal Angiogram	Tetraethyl- Ammonium Chloride Test (TEAC)	<sup>131</sup> I-Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder				
15	5/16/57	7 — 3.4	62 — 1	2 — ?	Right renal artery was narrowed 0.5 cm. from the aorta†		There was decreased vascularity on right	Patient refused operation  Unilateral renal arterial hypertension was suspected
		7 — 4.1	80 — 1.1	1.8 — ?				
	5/23/57	12 — 7.1	108 — 2.3	53 — 7.4				
		10 — ?	40 — 4	20 — 11.9				
16	6/1/57	15 — 6.2	40 — 2.3	7 — 6.2	Unsuccessful¶			Agenesis of left kidney was confirmed at operation
		4 — ?	117 — 2.1	4 — 9.3				
	6/1/57	18 — 5.2	170 — 3.0	14 — 5.4				
		Only one ureteral orifice found						
17		35 — 52	24 — 49	0 — 0		Depressor response		His blood pressure fell moderately after sympathectomy for essential hypertension. Renal arteries were normal
		23 — 76	33 — 80	0 — 0				

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

† Complication of angiography. Patient developed pleural effusion.

‡ Complication of angiography. Patient developed periaortic extravasation of dye.

¶ Complication of angiography.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (ml.) Sodium Concentration (mEq./L.)				Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	<sup>131</sup> I-Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder					
18		43	43	0		Normal renal arterial arteriozation	Depressor response		Contracted right kidney
		5.0	4.9						
		39	38	0					
		4.3	4.1						
19		15	6	11		Depressor response		Chronic urethritis. Essential hypertension?	
		54	57	42					
		27	19	13					
		98	99	98					
20		19	19	5		Depressor response		Essential hypertension?	
		39.6	38.8	?					
		25	29	9					
		22	22	45					
21		40	34	12		Depressor response	Impaired vascularity bilaterally	Hydronephrosis, left, mild; nephrolithiasis, left	
		—	—	—					
		12	14	10					
		32	30	15					
		10	11	12					
		34	35	25					
		8	9	10					
		65	59	0					
	2	2							

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions*			Translunbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	<sup>125</sup> I-Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder				
22		26.5	25.7	0		Depressor response	Normal	Essential hypertension?
		11	12					
23		24	26	0.25		Depressor response		Essential hypertension?
		11	10	?				
		20	23	1.0				
		55	57	?				
24		31	32	1.0	Normal renal arterio- arborization			Essential hypertension?
		22	20	?				
		38	32.5	1				
		8.7	8.1	1.0				
25		38.5	37.5	7	No renal arterio- arborization on left			Agenesis of left kidney was confirmed on exploration
		8.0	7.4	7.3				
26		Only one ureteral orifice found			Unsuccessful			Chronic pyelonephritis in needle biopsy. Autopsy was not granted
		50	20	30				
27		39	41	42	Normal renal arterio- arborization		Delayed vascular phase on right	Essential hypertension?
		15	13.5	Not recorded				
		75	48	Not recorded				
		30	32	Not recorded				
28		90	88		Normal renal arterio- arborization			Hematuria, cause undetermined. Essential hypertension?
		13	20	12				
		2	1.8	1.8				
		27	36	9				
		2.0	2.0	5				

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (ml.)				Translumbar Renal Angiogram	Tetraethyl-Ammonium Chloride Test (TEAC)	In-Labeled Diodrast Renogram	Remarks			
		Sodium Concentration (mEq./L.)		Bladder								
29		Right	Left			Normal renal arterial arborization. Nephrographic effect absent on left			Diabetes mellitus, chronic pyelonephritis, probable left renal infarct. Blood pressure spontaneously returned to normal			
		41	35	160								
		48	43	46								
		50	30	5								
30		47	27	15		Unsuccessful			Benign prostatic hypertrophy			
		7	8.5	Not recorded								
		Not recorded	Not recorded									
		Unable to catheterize bladder										
32	3/28/57	17	14	Not recorded	Normal renal arterial arborization		Bilateral delay in vascular phase. Sustained rise on right, suggesting obstructive phenomena	Chronic pyelonephritis				
		147	166									
	4/4/57	16	35	2								
		56	50	7								
33		6	19	0			Bilateral ischemic pattern, worse on right	At autopsy, no renal arterial lesions. Bilateral ureteroceles, hydronephrosis and chronic pyelonephritis. Necrotizing arteriolitis				
		74	67									
		43	37	0								
		28	14									
34		52	85	11			Impaired vascularity on right	Essential hypertension?				
		22	20	?								
		40	38	10								
		90	90	80								

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.

TABLE 1—(Continued)

Case No.	Date	Differential Renal Excretory Functions* Urine Volume (mL) Sodium Concentration (mEq./L.)				Translumbar Renal Angiogram	Tetraethyl- Ammonium Chloride Test (TEAC)	I <sup>131</sup> -Labeled Diodrast Renogram	Remarks
		Right	Left	Bladder					
35		9 — 97	620 — 77	Not recorded				Marked decreased vascularity on right, moderate on left	Normotensive. Hydronephrotic shell on right. Right nephrectomy
36	7/1956	44 — 74	55 — 72	66 — Not recorded				Bilateral ischemic pattern	Congenital stricture, ureteropelvic junction. Hydronephrosis, left
	9/1956	50 — 56	60 — 55	5 — Not recorded					
37		20 — 19 — 18 — 19	19 — 20 — 25 — 21	0.5 — ? — 0				Bilateral ischemic pattern. Obstructive uropathy pattern on right	Diabetes mellitus. Essential hypertension?
38		36 — 4.8 — 39 — 5.8	35 — 4.7 — 40 — 5.0	0.5 — ? — 3 — 1.2				Bilateral ischemic pattern	Essential hypertension?
39		20 — 10.8 — 31.5 — 10.4	29 — 14.9 — 2.7 — 14.4	0.5 — 5.0 — 2.0 — 14				Ischemic right pattern	Congenital ureteropelvic obstruction with unilateral hydronephrosis, right. To be reevaluated

\* Urine volume is expressed as the numerator and sodium concentration as the denominator.



repeat TEAC test gave a depressor response. Translumbar renal angiography disclosed impaired vascularity within the parenchyma of each kidney, but no lesions were seen in the main renal arteries. A radioactive renogram suggested impaired vascularity bilaterally, more marked in the left kidney. Repeat differential renal excretory function studies showed no significant difference in the urine volume and sodium concentration on the two sides (table 1).

Eight months after the initial series of tests the patient died. At autopsy there were an advanced degree of bilateral nephrosclerosis and a moderate degree of chronic pyelonephritis. No focal renal arterial lesion was found.

*Case 3.* A 44 year old woman was admitted for evaluation of hypertensive renal disease. For about five years she had experienced periodic right-sided backaches. Her blood pressure was normal six months prior to admission. Two months before admission she developed congestive heart failure, and her blood pressure was markedly elevated. Nine days prior to admission she was hospitalized elsewhere with acute pulmonary edema. Her blood pressure was 250-300/190-200 mm. Hg. Retrograde urography disclosed right hydronephrosis and hydro-ureter. Examination at time of transfer to this hospital revealed Keith-Wagener Grade 1 retinopathy, cardiomegaly, subsiding congestive heart failure, bilateral costovertebral angle tenderness, more marked on the left, and blood pressure of 200/110 mm. Hg in each arm. Serial urinalyses gave reactions varying from alkaline to acid, albuminuria of 1 to 3 plus, microscopic hematuria and pyuria, hyaline and granular casts, and maximal concentrating ability of 1.012. Blood chemical studies were normal. There was a leukocytosis of 13,500. An electrocardiogram was suggestive of anterolateral myocardial damage. Left ventricular enlargement and pulmonary congestion were found by x-ray. In an excretory urogram there was good concentration of dye in both kidneys but considerable dilatation and blunting of the right collecting system. The right kidney was 1.5 cm. smaller than the left. Differential renal excretory functions were performed on the fourth hospital day, the patient having been on a 500-mg. sodium diet (table 1). Retrograde urography following completion of excretory studies disclosed marked right hydronephrosis and hydro-ureter, with partial obstruction at the ureterovesical junction. An indwelling ureteral catheter was left in the right renal pelvis for three days, and during this period the patient's blood pressure fell from a mean of 180/100 mm. Hg to 140/80 mm. Hg.

Twelve days after the differential excretory functions, these studies were repeated (table 1). Three days later, translumbar renal angiography outlined only the proximal 2 cm. of the left renal artery, and it appeared to be occluded at this point (figure 1). Three small arteries led to the region of the left kidney, where a good nephrographic effect was noted in the upper pole. The right renal circulation was normal. A radioactive Diodrast renogram was interpreted as hydronephrosis on the right. Right ureteroneocystostomy relieved the obstruction.

Two and one-half months after her operation the patient was hospitalized for reevaluation, at which time she was asymptomatic, having lost 35 pounds. Her blood pressure was 130/80 mm. Hg. Differential renal excretory functions were repeated and are shown in table 1.

The patient was re-admitted one year later because of persistent pain in the right back and flank for one month. Physical findings were then normal except for obesity and tenderness in the right costovertebral angle. Her blood pressure was 120/80 mm. Hg. Laboratory data disclosed normal blood chemical findings, normal hemogram, normal electrocardiogram and normal-sized heart. Pyuria and bacteriuria with slight albuminuria persisted. The patient responded promptly to chemotherapy and increased fluid intake. She was discharged, to return for reevaluation when differential renal clearances were repeated (table 1). Four days later, translumbar

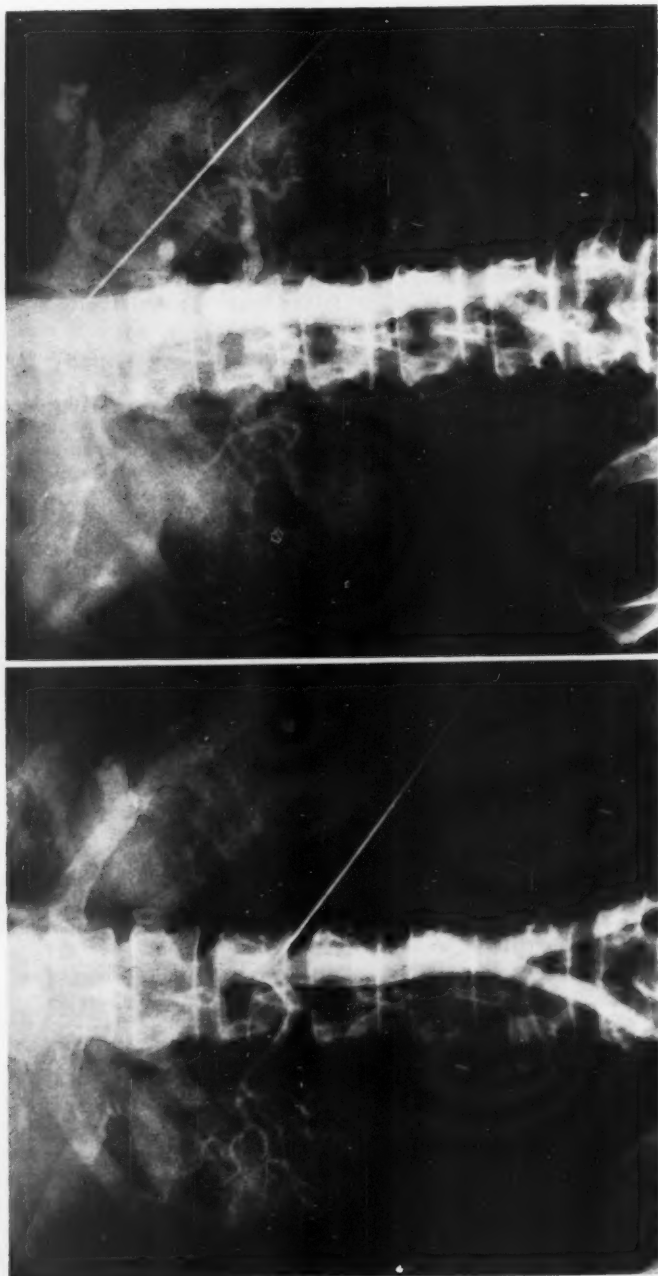


FIG. 1. Case 3. On the left is the angiogram obtained during the first admission. Note the obstruction in the arterial system of the left kidney. On the right is the angiogram obtained 18 months later, during the second admission. Note adequate filling of the vessels to both kidneys. See text for details.

renal angiography showed no abnormality of renal arterial circulation in either kidney (figure 1).

*Comment:* Case 3 was of particular interest for three reasons:

1. Unilateral ureteral obstruction was the probable cause of rapidly progressive, severe hypertension.

2. The initial differential excretory function test indicated that the normal left kidney was ischemic.

3. The initial renal angiogram disclosed apparent obstruction of the left renal artery. When the ureteral obstruction was relieved, the blood pressure returned to normal.

The remaining 64 patients, whose tests were satisfactory, showed no significant difference in the excretion of urine and sodium from the two kidneys (negative test). Nephrectomy resulted in no improvement in two patients, but in one patient malignant hypertension was reversed.

*Case 4.* A 56 year old housewife was hospitalized for evaluation of hypertension of 13 years' duration. She had been asymptomatic until three weeks prior to admission, when she experienced sudden right retro-orbital pain and transient dysarthria. There was no history of hypertension in her family. Physical findings at admission were moderate obesity, Keith-Wagener Grade 1 retinopathy, moderate cardiomegaly, and blood pressure of 240/160 mm. Hg. Laboratory studies revealed a normal hemogram, blood urea nitrogen of 21 mg.%, minimal albuminuria, rare granular casts, and maximal concentrating power to 1.020. An electrocardiogram was interpreted as left ventricular hypertrophy and strain. A TEAC test gave a depressor response. Moderate enlargement of the left ventricle was seen on x-ray. An intravenous urogram revealed prompt excretion of dye bilaterally, with a double collecting system on the right. Differential renal excretory functions were essentially equal from the three collecting systems (table 1). Translumbal renal angiography outlined a normal single right renal artery supplying the double collecting system; there were two small left renal arteries, the upper of which appeared to be normal. The left lower renal artery was slightly narrowed at its origin, and its arborization was less abundant than that of the left upper artery (figure 2). A radioactive renogram showed less vascularity in the left, but both curves were within normal ranges.

At operation, two arteries were seen to be supplying the left kidney, and both were pulsating. Left nephrectomy did not alter the blood pressure. The surgical specimen revealed moderately advanced arterio- and arteriolar nephrosclerosis, chronic pyelonephritis, and marked generalized narrowing of the lumina of the arteries.

*Case 5.* A 37 year old woman was admitted for surgical treatment of hypertension considered to be of unilateral renal origin. There was no family history of hypertension. Although hypertension had been discovered at age 18, the patient had remained asymptomatic until the onset of headaches and mild edema two and one-half years earlier. Because of these symptoms she was hospitalized elsewhere, and was found to have persistent hypertension, averaging 210/120 mm. Hg, Keith-Wagener Grade 1 retinopathy, cardiomegaly, and electrocardiographic evidence of left ventricular hypertrophy and strain. An intravenous urogram was normal, although the left kidney was slightly smaller than the right. Differential renal excretion studies showed diminished urine volume, but slightly higher sodium concentration on the left (table 1). Six months before admission, differential renal function studies were unchanged. Marked narrowing of the left renal artery, with

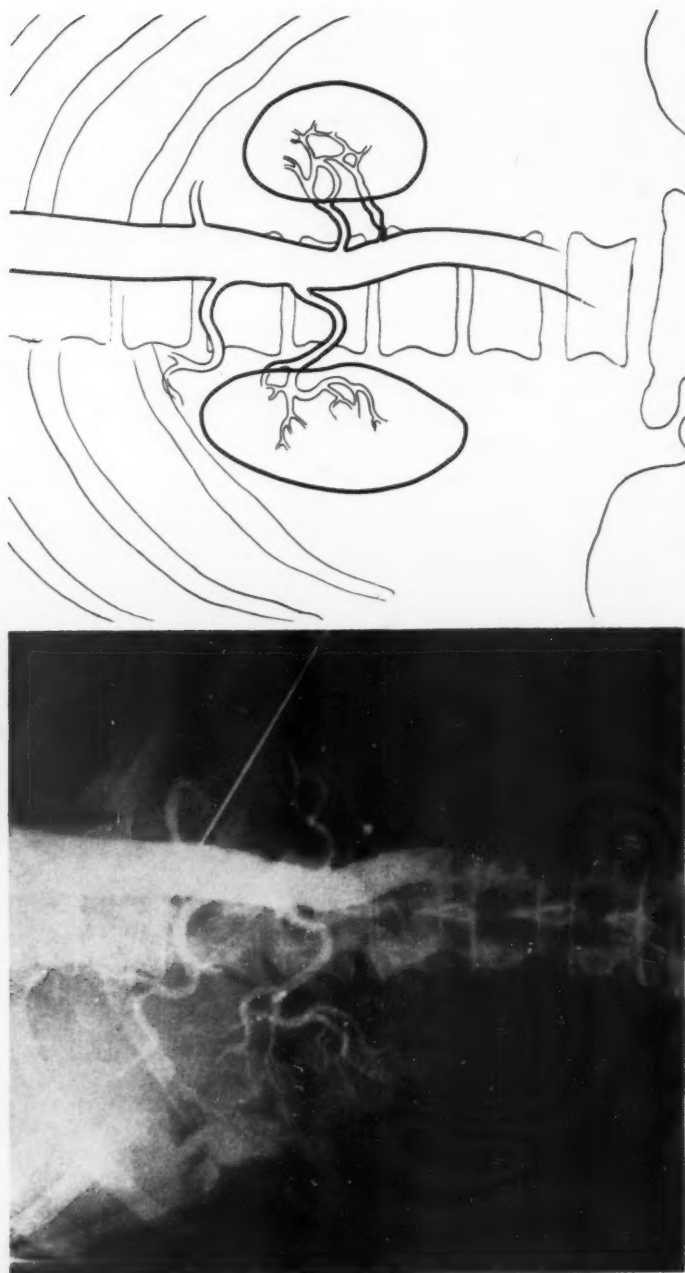


FIG. 2. Case 4. Translumbar angiogram. The detailed findings are more clearly outlined in the drawing on the right. Note the narrowing of the lower artery leading to the left kidney. See text for details.

considerable decrease in its vascular pattern, was seen in the renal arteriogram. The left kidney was 3 cm. smaller than the right. On admission the patient's physical findings were unchanged. Her blood chemical studies, hemogram and urinalyses were normal. A radioactive renogram indicated impaired renal blood flow in the left kidney. At operation, an artery entering the lower pole of the left kidney was thickened. Beyond this area no pulsations were felt. This artery was found to contain a clot without point of attachment or evidence of organization. Two additional renal arteries supplied that kidney and were patent. Nephrectomy did not alter her hypertension.

*Case 6.\** A 35 year old woman was hospitalized because of recurrent hypertension. At age 30 she had developed malignant hypertension. An aberrant artery supplying the lower pole of the left kidney had been occluded by retrograde propagation of the thrombus of a Leriche syndrome. Following thrombo-endarterectomy and left heminephrectomy, her blood pressure returned to normal until six months prior to admission. Then hypertension recurred, and rapidly progressed to a malignant phase. A TEAC test produced a pressor response. Translumbar renal angiography showed an avascular lower pole of the right kidney, interpreted as occlusion of an aberrant artery. Differential renal function studies were normal (table 1). The patient's blood pressure returned to normal following right heminephrectomy. The TEAC test was repeated postoperatively and remained pressor. Eighteen months after operation the blood pressure was normal.

*B. Unsatisfactory Tests.* Differential ureteral catheterization studies were unsatisfactory in 55 patients. Nephrectomy in four patients of this group was associated with reversal of hypertension in three and symptomatic improvement in one, who had only systolic hypertension.

*Case 7.* A 34 year old housewife was hospitalized for hypertensive evaluation. There was no familial history of hypertension. Three and one-half years before admission she had developed hypertension during active labor with her second pregnancy. This hypertension persisted and was associated with frequent occipital and frontal headaches. On admission the only abnormal finding was a blood pressure of 220/120 mm. Hg. Laboratory investigations disclosed a normal hemogram, normal blood chemical tests, normal urinalyses, and the ability to concentrate urine to 1.023. The electrocardiogram was normal. Chest x-ray revealed a normal-sized heart. An excretory urogram showed a delayed appearance of dye in the right kidney, which was 4.0 cm. smaller than the left. A 30-minute study of differential renal excretion disclosed no urine from the right kidney, a "nonfunctioning" kidney, while 62 ml. of urine were obtained from the left (table 1). Translumbar renal angiography disclosed equal arborization in each kidney but a narrowing of the mid-portion of the right renal artery. This test was complicated by development of bilateral pleural effusions. Because of this, the patient was discharged to return for surgery following convalescence.

Right nephrectomy was performed one month later. The blood pressure slowly declined to normal over the initial five postoperative days, and has remained normal for three and one-half years. At operation the obstructive lesion in the right renal artery was inaccessible because of its proximity to the aorta. Distal to the narrowing, the artery was smaller than normal, but pulsations were present.

*Case 8.†* A 48 year old man was hospitalized for evaluation of accelerated hypertension of recent onset. There was no family history of high blood pressure. An excretory urogram disclosed delayed appearance time of dye in the right kidney.

\* This case to be reported in detail by Dr. Leonard Scherlis.

† Case 8 will be reported in detail by Dr. T. B. Connor.

which was 1.5 cm. smaller than the left. A TEAC test gave a depressor response. Differential renal studies during two collection periods are shown in table 1. The test was unsatisfactory because of urine volumes of less than 1.0 ml. on the right. Translumbar renal angiography disclosed narrowing of right renal artery 1 cm. distal to its origin. Beyond the point of narrowing the artery was dilated and contained an area of radiolucency. A radioactive renogram was abnormal, suggestive of impaired blood flow in the right kidney.

This patient's blood pressure gradually returned to normal following right nephrectomy, and was 150/90 mm. Hg 16 months later.

*Case 9.* A 44 year old man was admitted for evaluation of hypertension. He had been well until six months prior to admission, when he noted nocturia, and one month later developed headaches. Seven weeks prior to admission an ophthalmologic examination (because of these headaches) disclosed normal vision and normal optic fundi. During this interval there was a loss of 20 pounds, associated with persistent fatigue, and four weeks before admission the patient suddenly developed weakness in his legs. Two weeks before admission he was referred to an internist, who found exudates in both retina, a blood pressure of 200/120 mm. Hg, and 1 plus albuminuria, with occasional hyaline and cellular casts. In the week prior to admission he developed a yellow tint to his vision, and rapidly progressive loss of visual acuity.

Admission examination showed a slightly drowsy male, Keith-Wagener Grade 4 retinopathy with five-diopter elevation of the nerve head, normal cardiac examination except for sinus tachycardia, and a blood pressure of 192/120 mm. Hg. Neurologic examination disclosed generalized motor weakness, particularly in the left leg, with occasional clonic muscular contractions in both legs, and hyperactive deep reflexes with unsustained clonus in the left ankle. Toe signs were equivocal and changeable; sensory examination and coordination were intact. Laboratory studies showed normal blood chemical tests, specific gravity ranges of 1.008 to 1.011, 2 to 3 plus albuminuria, occasional hyaline and granular casts, and a white blood count of 12,950, with a normal differential count. X-ray examination of the heart was normal. An electrocardiogram was interpreted as left ventricular hypertrophy in a vertical heart. An intravenous urogram showed prompt appearance of the dye bilaterally; the cortex of the right kidney appeared to be somewhat thin. The right kidney was 2.3 cm. smaller than the left. Differential renal function studies were unsatisfactory because of decreased urine flow and failure to record bladder leakage (table 1). On the eighth hospital day a translumbar renal arteriogram was done, using 12 ml. of 70% Urokon. Arborization of the vessels in the right kidney was less abundant than in the left. There was a marked nephrographic effect in the right kidney which was absent in the left. A second injection of 10 ml. of 70% Urokon provided no better vascularization.

Higher sodium concentration and no apparent renal arterial obstruction on the involved side failed to support the initial clinical impression of unilateral renal artery occlusion. Progressive loss of vision and motor weakness in the patient's legs led to a decision to proceed with lumbodorsal sympathectomy and adrenalectomy. Right transthoracic sympathectomy from T-5 to L-2 was performed. When the right kidney was exposed, it was discolored in its upper and anterior two thirds, and the main renal artery was occluded by a mass distal to its bifurcation. There was no detectable blood flow beyond the point of occlusion. The smaller branch supplied the posterior inferior pole. The right kidney and adrenal were removed.

The postoperative course was marked by a hypotensive period lasting for 20 hours, during which the patient's vision failed to only light perception. The neurologic involvement progressed to complete motor and sensory loss below D-9 and has persisted. Visual acuity gradually improved over a period of one year, so that following rehabilitation the patient was able to return to his duties as an auditor. His blood pressure has remained normal for five years, never exceeding 140/90 mm. Hg.



*Case 10.* A 59 year old woman was hospitalized for evaluation of pyuria and elevated systolic blood pressure. Ten years prior to admission a right renal calculus was discovered incidental to surgery for cholelithiasis. Six months before admission the patient had experienced interscapular pain with exertion, which had increased in severity. One month prior to admission she was found to have elevated blood pressure and pyuria. On examination she was found to have mild atherosclerotic retinal changes, a soft aortic systolic murmur, and a blood pressure of 180/80 to 185/85 mm. Hg. Pertinent laboratory studies revealed a urea nitrogen of 20 to 26 mg.%, normal hemogram, urine specific gravity of 1.005 to 1.026, alkaline to acid reaction, albuminuria of 1 to 3 plus, and pyuria. *Escherichia coli* was cultured from her urine. Calcification in the aortic arch and left ventricular enlargement were seen on chest x-ray. An intravenous urogram revealed marked nephrolithiasis and hydronephrosis on the right, with nonobstructive right ureteral calculi. An electrocardiogram showed changes consistent with anterior myocardial damage. Differential renal function studies were not satisfactory because of the small volume, and bladder leakage was not recorded (table 1). The right kidney was removed. Post-operative blood pressure readings have ranged from 140/70 to 178/80 mm. Hg, averaging 158/80, and the patient has remained asymptomatic.

*2. Translumbar Renal Angiography:* Translumbar renal angiography was employed in studying 24 patients in our series (table 1). Renal arterial circulation was considered to be normal in 10, abnormal in 10, and unsatisfactory in four patients.

In the group whose angiograms were normal, normal tests were confirmed in two patients at operation (case 12) or autopsy (case 13).

Four of the 10 patients whose angiograms were interpreted as abnormal deserve comment. In case 3, the initial renal angiogram showed obstruction of the left renal artery. When repeated 18 months later, it was normal (figure 1). In case 9, diminished arborization and marked nephrographic effect were seen in the right kidney. The right renal artery was initially considered to be normal. When reviewed after operation, it was observed that 1.25 cm. distal to its origin the right renal artery bifurcated and the larger branch was completely occluded. In case 5, angiography showed narrowing of the left renal artery with decreased arborization. A small aberrant artery supplying the upper pole was not identified. Narrowing of the artery to the lower pole was confirmed at operation, but nephrectomy failed to correct hypertensive cardiovascular disease. Narrowing of an artery supplying the lower pole of the left kidney, as demonstrated in renal angiography in case 4 (figure 2), was not confirmed at operation, and blood pressure was not affected by nephrectomy.

The complications encountered in this small group have curtailed use of this test in many hypertensive patients.

Serosanguineous pleural effusion was a complication in three patients (cases 7, 14 and 15), and periaortic extravasation occurred in one (case 16). In case 9, permanent paraplegia followed translumbar renal angiography, but there was abundant evidence of antecedent widespread vascular necrosis and central nervous system involvement. One death resulted from a severed intercostal artery (case 11).

*Case 11.* This 51 year old man was admitted for evaluation of hematuria. When he had been hospitalized four years previously because of prostatic obstruction, his blood pressure had been 190/120 mm. Hg, and his urea nitrogen, 76 mg.%. Following retropubic prostatectomy, his blood pressure gradually fell to 130/90 mm. Hg, and his urea nitrogen to 24 mg.%. Seven months prior to his second admission he developed congestive heart failure and was found to have a blood pressure of 190/130 mm. Hg, a urea nitrogen of 25 mg.%, and phenolsulfonphthalein excretion of 15% in 15 minutes. Two weeks before admission he noted painless hematuria. On admission he was found to have a blood pressure of 230/160 mm. Hg, Keith-Wagener Grade 3 retinopathy, cardiomegaly and hepatomegaly. Urine was grossly bloody, and urea nitrogen was 110 mg.%. Intravenous urography failed to visualize the right kidney, and there was very poor visualization of the left calyceal system. A retrograde urogram showed a small right kidney without evidence of obstruction. Technical difficulties prevented catheterization of the left ureter. Translumbar renal angiography was attempted. The patient died shortly after this procedure. At autopsy there was a massive hemopneumothorax which had collapsed the left lung. An intercostal artery was severed. Fresh blood surrounded a 3 mm. hole in the posterior aortic wall at the site of an atherosclerotic plaque. The left renal artery was approximately 75% occluded by a recent thrombus, and the right kidney was contracted by unilateral chronic pyelonephritis. The right kidney weighed 60 gm. and the left, 200 gm.

*3. Tetraethylammonium Chloride Test:* TEAC tests were done on 11 patients in our series. A pressor response was obtained in two. In case 6, the TEAC test was positive prior to right heminephrectomy and remained positive during convalescence, after the blood pressure had returned to normal. A pressor response was initially observed in case 2; when repeated two months later there was a depressor response. No renal arterial lesion was found at autopsy.

A TEAC test gave a depressor response in two patients on whom a nephrectomy was done. In case 4, no renal arterial lesion was found at operation, and removal of the left kidney did not alter the blood pressure. In case 8, the right renal artery was partially occluded by a thrombus, and the blood pressure returned to normal following nephrectomy.

In seven additional patients, depressor responses were obtained with the TEAC test. No cause for their hypertension was found.

*4. I<sup>131</sup>-Labeled Diodrast Renograms:* Radioactive renograms were not employed to screen hypertensive patients for unilateral renal disease. The Radioisotope Laboratory of this hospital was conducting a study of I<sup>131</sup>-labeled Diodrast renograms, and 19 patients in our series were included in their study.

Normal bilateral radioactive renograms were obtained in two of the 19 patients (cases 4 and 22). No renal cause for their hypertension was found by other investigations.

Abnormal unilateral isotopic renograms were recorded in seven patients. Two of these were found to have renal arterial lesions at operation (cases 5 and 8), one of whom was cured by nephrectomy. One patient (case 15) was considered to have a unilateral renal arterial lesion, but refused opera-

tion. Unilateral obstructive uropathy was found in two (cases 3 and 39). The remaining two patients with abnormal unilateral renograms (cases 27 and 34) were considered to have essential hypertension.

Abnormal bilateral radioactive renograms were obtained in 10 patients. Chronic pyelonephritis was found on biopsy or at autopsy in four (cases 2, 13, 32 and 33), and suspected in three additional patients (cases 21, 35 and 36) who had unilateral hydronephrosis and pyelonephritis. Three patients considered to have essential hypertension had some impairment of excretory renal function in addition to abnormal bilateral isotopic renograms (cases 14, 37 and 38).

### DISCUSSION

Differential renal excretion of urine and its sodium concentration was satisfactorily measured in only one-half of the patients in whom it was attempted. Most of the unsatisfactory tests occurred in the first year of this study, and were due to a variety of causes. Inadequate urine volume, failure to record bladder leakage, or a combination of both, accounted for 27 of 55 unsatisfactory tests. Urine sodium concentration below 10 mEq./L. made the test unsatisfactory in 17 patients, most of whom were on sodium-restricted diets. The test was unsatisfactory in four patients because of excess leakage into the bladder, and in three patients it was not possible to catheterize both ureters. In two patients the test was unsatisfactory because urine flow from one kidney was less than 1.0 ml., while more than 60 ml. were excreted by the other, a "nonfunctioning kidney."<sup>5</sup> Sodium contaminated glassware and gross hematuria each accounted for one unsatisfactory test.

Studies of the excretion of urine and sodium were accurate in predicting the outcome of nephrectomy in two patients. Negative tests (cases 4 and 5) correctly foretold that there would be no improvement from nephrectomy. A "nonfunctioning kidney" on one side made the test valueless in predicting the outcome in two patients (cases 7 and 8).

False-positive differential excretory function tests occurred in one patient with chronic pyelonephritis (case 2) and one with unilateral ureteral obstruction (case 3). A positive test in case 1 was neither verified nor rejected. There was one false-negative test (case 6). In one patient (case 9), the test was unsatisfactory but probably false because of higher concentration of sodium on the involved side.

Translumbar renal angiography was not an innocuous procedure. Some complication developed in one quarter of the patients tested, including one who died (table 1).

A false-positive angiogram was obtained in case 3 and probably in case 4. A narrowed renal artery was confirmed at operation in one patient (case 5) who was not improved by nephrectomy.

Tetraethylammonium chloride tests were not reliable in predicting the

presence of unilateral renal arterial lesions. The test was negative in one patient (case 8) with proved renal artery obstruction, and initially positive in a patient (case 2) without a renal artery lesion.

Winter<sup>9</sup> suggested that radioactive renograms could be used in screening hypertensive patients for unilateral renal disease. In the patients studied to date, no patient with a normal radioactive renogram has been found to have renal hypertension. Abnormal unilateral renograms may occur in patients with a variety of renal lesions (table 1, cases 3, 5, 8, 15, 27, 34 and 39).

Comparative results of these four tests in 12 patients whose diagnoses were reasonably certain are shown in table 1. The tests agreed in four patients (cases 12, 13, 17 and 33). None of these had unilateral renal hypertension.

There were five patients whose unilateral renal hypertension was ameliorated by surgery. Comparison of test results was not possible in case 7 because of a "nonfunctioning" right kidney. Initial false-positive results implicated the wrong kidney in a patient with unilateral ureteral obstruction (case 3). Contradictory results were obtained in two patients (cases 6 and 8). Results were probably conflicting in case 9 because of the higher sodium concentration on the involved side.

Contradictory results were obtained in two patients who were not benefited by nephrectomy (cases 4 and 5), and in a patient with bilateral renal disease (case 2).

#### SUMMARY

1. Studies of the differential excretion of urine and sodium require meticulous attention to technical details. False-negative and false-positive results may be obtained in patients with reversible unilateral renal hypertension. Caution must be exercised in interpreting results.

2. Renal angiography is not an innocuous test. False-positive renal angiograms may occur, and demonstration of renal arterial narrowing does not necessarily indicate correctable renal hypertension.

3. Tetraethylammonium chloride (TEAC) tests may give false-positive and false-negative results in patients with unilateral renal hypertension.

4. There is as yet no completely reliable test to detect correctable renal hypertension.

5. Continued investigation of these tests is necessary before their value can be accurately assessed.

#### ACKNOWLEDGMENTS

The authors are indebted to Dr. John M. Dennis and his colleagues, Department of Radiology, University of Maryland, for their able assistance in interpreting the radiologic studies performed on these patients. Grateful acknowledgment is also made to the many Fellows who have participated in these studies, to Dr. T. E. Woodward for permission to study case 4, and to Dr. Leonard Scherlis and Dr. T. B. Connor for permission to include the data from cases 6 and 8.

Some of the data from cases 4, 5 and 6 were reported by T. B. Connor, W. C. Thomas, Jr., L. Haddock and J. E. Howard, *Ann. Int. Med.* 52: 544, 1960.

## SUMMARIO IN INTERLINGUA

Con le objectivo de deteger reversibile hypertension de origine reno-unilateral, un o plure tests special esseva effectuate in 122 casos. Le mesuration differential del excretion del renes de urina e del correspondente contentos urinari de natrium esseva tentate in omne le casos. In circa un medietate le resultados obtenite esseva satisfactori. In tres de iste casos, le tests esseva positive, suggerente le presentia de reversibile hypertension de origine in morbo reno-arterial de un latere. In duo, le positivitate esseva false. In le tertie caso, le patiente refusava omne altere studios. In un caso le test esseva falsemente negative. In illo le patiente esseva un femina con infarimento segmental del ren al latere dextere in qui le hypertension esseva curate per heminephrectomia. Le negativitate del test esseva confirmate in duo patientes in qui nulle melioration resultava del ablation de un ren con levemente restringite arterias renal.

Angiographia renal translumbar non se revelava como un manovra innocue. Complicationes occurreva in un quarto del 24 patientes in qui iste studio esseva executate. Un de istos moriva in consequentia del section de un arteria intercostal. Un del angiogrammas renal esseva falsemente positive, e in un altere caso un demonstrabilemente restringite arteria renal esseva confirmate al operation. Le patiente in iste caso esseva un femina in qui nulle melioration esseva obtenite per le nephrectomia.

Tests a chloruro de tetraethylammonium non esseva digne de confidentia como indicadores de reversibile hypertension de origine reno-arterial de un latere. In un serie de 11 patientes, le test esseva un vice falsemente positive e un vice falsemente negative.

Renogrammas con Diodrast a  $I^{131}$  esseva obtenite in solmente pauc casos, de maniera que nulle evaluation es possibile.

A iste tempore, il existe non ancora un completamente fidel test pro deteger corrigibile hypertension renal. Continue investigationes de iste tests es necessari ante que lor valor pote esser fixate accuratamente.

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## PROPHYLACTIC HEMODIALYSIS IN THE TREATMENT OF ACUTE RENAL FAILURE\*

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### INTRODUCTION

FOLLOWING the introduction of clinically usable artificial kidneys by Kolff,<sup>1</sup> Alwall,<sup>2</sup> Murray<sup>3</sup> and Skeggs and Leonards,<sup>4</sup> and the pioneering clinical investigations by Merrill,<sup>5,6</sup> hemodialysis has been widely employed in the treatment of acute renal failure § according to certain conventional indications: (1) definite clinical uremia, and/or (2) hyperkalemia with myocardial potassium intoxication, when either or both progress in spite of a suppressive medical regimen, including cation exchange resins for potassium removal.<sup>7-15</sup> Such dialysis treatment usually results in a more nearly normal blood chemical pattern and a gratifying clinical improvement, at least in the absence of significantly symptomatic underlying disease.<sup>16</sup> The latter is vitally important because underlying sepsis, hypoxemia and a variety of other states sometimes mimic the uremic syndrome itself.<sup>17,18</sup> Unless diuresis and renal function return, however, the improvement is transient, and repeated dialyses on the same indications produce the familiar, fluctuating chemical and clinical course<sup>19</sup> (figure 1).

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§ In this presentation, patients with acute renal failure are identified by oliguria, urinary volume of less than 400 ml./24 hours, with a compensated circulation, patent renal vascular supply, and patent postrenal urinary tract, in the absence of significant chronic renal disease. The phases of acute renal failure are further defined as follows: The oliguric phase is characterized by urinary volume of less than 400 ml./24 hours; the oliguric phase continues until the urinary volume equals or exceeds 1,000 ml./24 hours. The day on which this first occurs is termed, for convenience, the "day of diuresis." The "early diuretic phase" begins on the day of diuresis and continues until the day on which azotemia reaches its peak. The latter is the first day of the "late diuretic phase." The late diuretic phase ends on the day that the declining nonprotein nitrogen reaches 30 mg.%. The recovery phase begins at that time. Other workers have defined these terms in a variety of other ways; the conclusions drawn from the experience reported here do not appear to be affected by such differing definitions, however. "High output acute renal failure" refers to the situation in which acute renal failure with significant azotemia is associated with urinary volume greater than 400 ml./24 hours, i.e., those instances in which oliguria does not occur.



When hemodialysis is used in treatment, clinical uremic illness is generally easier to control. However, a clear reduction in mortality has been difficult to demonstrate. Mortality remains high among patients who have been referred to centers for possible dialysis treatment, especially among patients who develop conventional indications for dialysis and are so treated. As emphasized by Bluemle,<sup>20</sup> the data in table 1 (which presumably already reflect the beneficial effect of dialysis) contrast starkly with the inference that acute renal failure is a benign disease with a low mortality when it is properly treated,<sup>8,9</sup> even by medical measures alone.<sup>26</sup> Attentive reading reveals that published optimism about prognosis is carefully reserved, how-

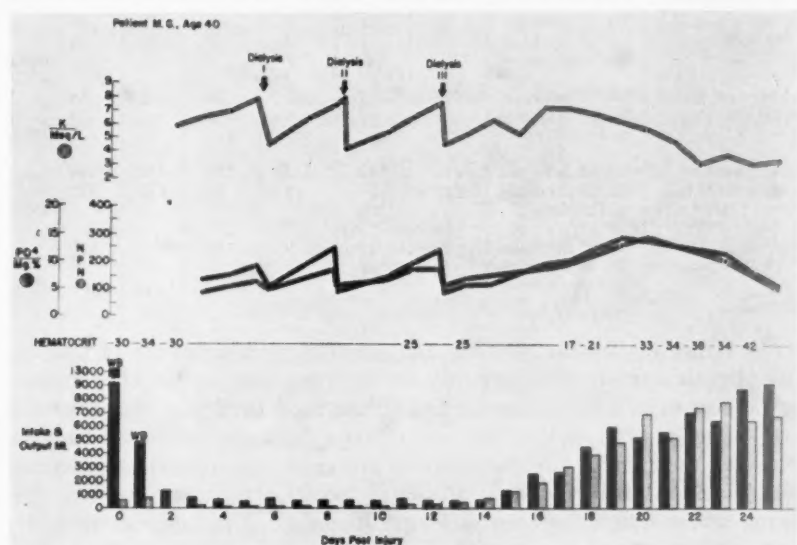


FIG. 1. Data from a 40 year old patient with acute renal failure following accidental trauma. Bringham-Kolff rotating drum dialyzer was used three times, with chemical and clinical benefit.

ever, for the "uncomplicated" cases. In our experience, instances of uncomplicated acute renal failure have been rare.

Instead, regardless of dialysis treatment, wasting, anemia, sepsis (especially pneumonia), and delayed healing of wounds occur frequently in patients with acute renal failure.<sup>20,27</sup> While these are most conspicuous in traumatized patients,<sup>27</sup> they are often found in fatal cases, regardless of the cause of the renal failure, and appear to cause death in many instances.<sup>20</sup> In contrast, such "complications" are rare in the larger number of patients who do not develop acute renal failure (or who develop milder forms, e.g., "high output" acute renal failure) in similar etiologic settings, such as surgical or accidental trauma, hemolytic transfusion reactions, exposure to poisons,

TABLE 1  
Acute Renal Failure—Mortality Rates

Author		Post-traumatic	Transfusion Reaction	Nephrotoxin	Post-Obstetric	Other	Total
Swan, Merrill (1953) <sup>21</sup>	No. of patients	19	27	17	6	16	85
	No. of fatalities	12	10	5	1	9	37
	% Fatalities						44%
Alwall (1954) <sup>22</sup>	No. of patients	33	5	0	8	16	62
	No. of fatalities	17	0	0	1	1	19
	% Fatalities						31%
Anthonisen et al. (1956) <sup>23</sup>	No. of patients	14	1	2	1	17	35
	No. of fatalities	10	1	2	0	11	24
	% Fatalities						68%
Palmer and Henry (1957) <sup>24</sup>	No. of patients	15	2	16	19	2	54
	No. of fatalities	?	?	6	?	?	?
	% Fatalities						50%
Study group on acute renal failure (1957) <sup>25</sup>	No. of patients	242	142	137	270	253	1,044
	No. of fatalities	160	56	44	82	170	512
	% Fatalities						49%
Bluemle et al. (1959) <sup>26</sup>	No. of patients	38	24	9	16	13	100
	No. of fatalities	28	7	5	4	6	50
	% Fatalities						50%

etc.<sup>27</sup> Hence the anemia, wasting and impaired wound healing in patients with oliguric acute renal failure may not be "complications" at all. Rather, they appear to be a part of acute renal failure itself (and possibly of chronic renal failure as well), in that they may reflect a damaging influence of uremia on many recuperative or homeostatic processes and physiologic defense mechanisms. Furthermore, in all series, occasional patients survive following severe trauma or even prolonged oliguria. This suggests that virtually all instances of acute renal failure must be considered to be reversible, even though oliguria may persist for three weeks or longer, and that mortality, like severe morbidity, should somehow be avoidable in a larger proportion of these patients.

#### HYPOTHESIS

Accordingly, for patients with acute renal failure (and possibly for chronic renal failure as well), the following postulates formed the basis of this investigation:

1. The uremic syndrome is often largely reversible by dialysis procedures.
2. Uremic patients frequently develop sepsis and other complications which are not reversible by dialysis and commonly cause death.
3. These complications may reflect a cumulative injury of many tissues

by the same toxic, dialyzable substances that presumably produce the uremic syndrome.

4. Therefore, prophylactic dialysis, applied before uremic symptoms appear, should prevent both the uremic syndrome and many of its commonly lethal sequelae.

#### MATERIALS AND METHODS

*Patients:* This report deals with our initial experience in testing this hypothesis in the first 15 patients who were referred to the Renal Center, U. S. Army Surgical Research Unit, for treatment of oliguric acute renal failure, and who could be treated with a series of prophylactic hemodialyses before the nonprotein nitrogen reached 200 mg.%\* and obvious symptoms

TABLE 2  
Clinical Data on Patients Treated with Prophylactic Hemodialysis

Patient	Age Sex	Etiology	Post-onset Day of Admission	Outcome
A. Acute Tubular Necrosis				
1	19 M	Heat stroke	3	Survived
2	25 F	Cardiac arrest and hemorrhage at and after closure of intra-atrial septal defect; vasopressors for 48 hours postoperatively	4	Survived
3	23 M	Traumatic rupture of spleen	4	Survived
4	23 M	Stab wound, left chest, laceration of pulmonary artery	6	Survived
5	30 M	Carbon tetrachloride poisoning	3	Survived
6	30 F	Self-induced abortion	5	Survived
7	21 M	Fractures of ribs, femur, tibia in motorcycle collision	3	Survived
8	47 F	Hemolytic transfusion reaction	3	Died suddenly with ventricular arrhythmia
9	35 F	Hemolytic transfusion reaction	2	Survived
10	37 M	Crushing injury with fractures, both lower legs	3	Died; intracerebral hemorrhage and necrosis; fat embolism
11	27 M	Epigastric shotgun wound, requiring 60% gastrectomy, left nephrectomy, splenectomy, excision of splenic flexure of the colon, repair of lacerations of small bowel vessels and liver, partial pancreatectomy	4	Survived
12	25 M	Multiple arm and leg fractures; auto accident	5	Died following aspiration of gastric contents; total (lt.) and partial (rt.) renal infarction due to renal artery thrombosis; infarcts and lacerations of spleen and liver
B. Bilateral Renal Cortical Necrosis				
13	27 F	Abruptio placentae	5	Died; sudden fall in blood pressure
14	35 F	Abruptio placentae	9	Died; sudden fall in blood pressure
C. Acute Glomerulonephritis				
15	4 M	Pharyngitis due to group A, Type 12 streptococcus	4	Survived

\* The initial nonprotein nitrogen was higher in one of the two patients with bilateral renal cortical necrosis; this patient is included, however, because of the unusual amount of information she contributed.

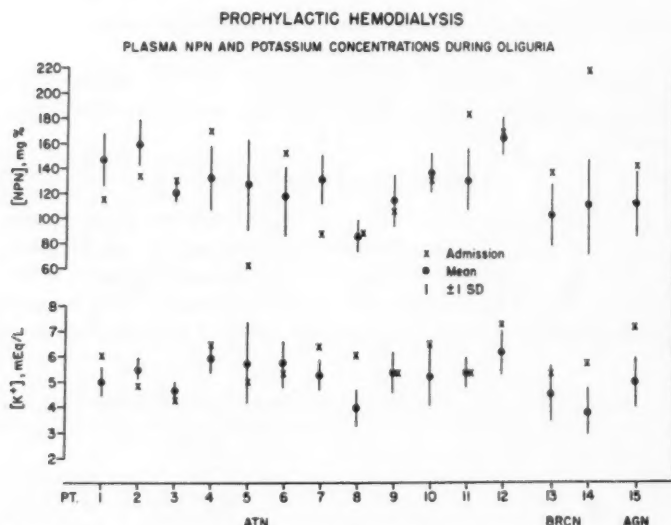


FIG. 2. Nonprotein nitrogen and potassium concentrations during oliguria in 15 patients with acute renal failure treated with prophylactic hemodialysis. Points represent the means, and vertical bars span  $\pm 1$  standard deviation of each sample ( $s = \sqrt{\frac{[\sum Y^2 - (\sum Y)^2/n]}{n-1}}$ ). Values on admission to the Renal Center are noted for each patient by (X).

of uremia appeared.<sup>†</sup> Pertinent data are summarized in table 2 and figures 2, 3 and 4. Twelve of these patients had acute tubular necrosis, six of them following severe trauma; two had bilateral renal cortical necrosis; and one, a four year old boy, had acute poststreptococcal (Group A, type 12) glomerulonephritis. In aggregate, during 398 oliguric days they were treated with 193 dialyses, each lasting approximately six hours, either daily, or often enough to maintain the nonprotein nitrogen below 150 mg.%.<sup>‡</sup> Because much of the clinical response of these patients could not be quantitated, color-sound cinematography was used in some instances to document clinical interviews and examinations.

**Dialyzers:** Both MacNeill-Collins § and Travenol || twin-coil dialyzers were used. The dialyzers and circuits were usually assembled, filled with compatible blood and operated by an Army enlisted Clinical Technician (one Technician per patient) under a physician's direct supervision.

**Clinical Management:** The dialyses were used in conjunction with a basic medical regimen which included the following:

<sup>†</sup> A preliminary report of initial findings has been published.<sup>28</sup>

<sup>‡</sup> This value does not imply an optimal level. It is possible that lower nonprotein nitrogen levels might be desirable, or that higher levels may be compatible with similar results.

§ Manufactured by Warren E. Collins, Inc., 555 Huntington Ave., Boston 15, Massachusetts.

|| Manufactured by Baxter Laboratories, Morton Grove, Illinois.

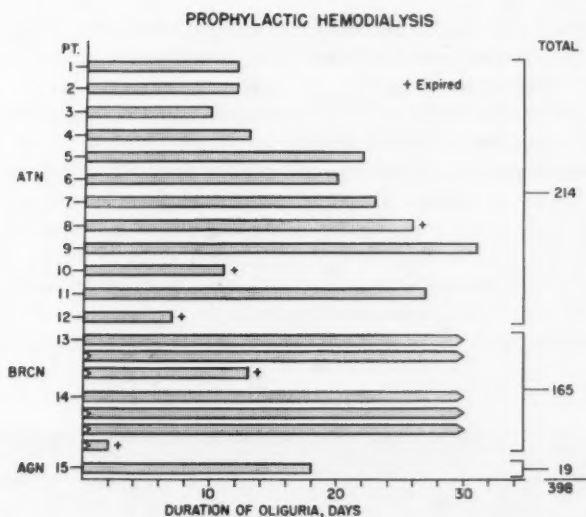


FIG. 3. Duration of oliguria in 15 patients with acute renal failure treated with prophylactic hemodialysis.

1. Fluid intake during oliguria was restricted to from 300 to 400 ml. per day in excess of measured losses. This allowance was frequently liberalized when ultrafiltration during dialysis was used to increase extrarenal fluid losses. During diuresis, *ad libitum* fluid intake was permitted.

2. Each patient selected a diet from the hospital menu, unrestricted in amount or composition, and including protein and potassium-containing foods *ad libitum*. Carbohydrate-fat mixtures were specifically avoided,

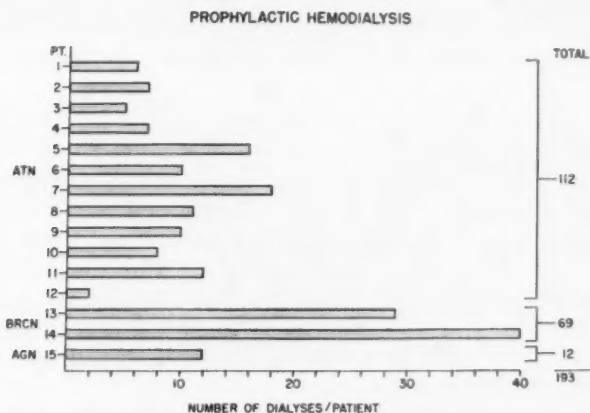


FIG. 4. Number of dialyses employed prophylactically in 15 patients with acute renal failure.

since a balanced diet might be needed to supply essential nutrients subject to depletion by dialysis; on the other hand, metabolites in excess of needs would be removed by dialysis.

3. Ambulation was vigorously encouraged between dialyses in patients not confined to bed by associated disease.

4. When present on admission, indwelling urethral catheters were removed and were not used. Blood which would flow spontaneously from the dialyzer and/or that remaining from the initial priming was usually given to the patients during or following each dialysis. The few drugs used were given in reduced, stat doses; antibiotics were given only on specific indication, in doses adjusted according to their probable loss by dialysis.<sup>29</sup> Other measures have been well discussed in innumerable publications in this field.

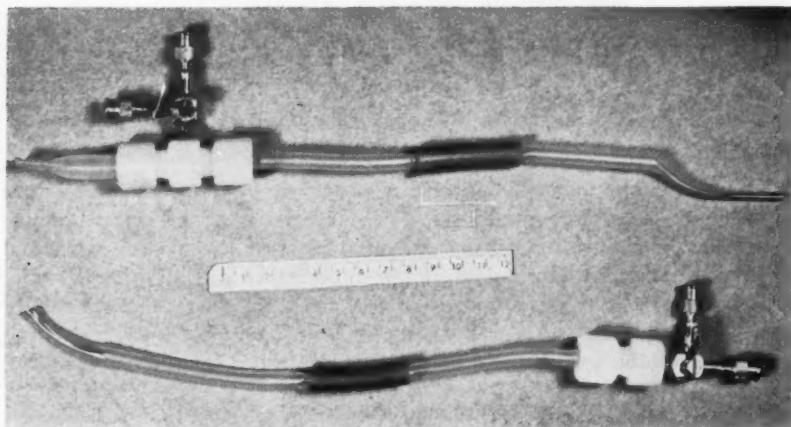


FIG. 5. Plastic cannulae fitted for chronic vessel cannulation and heparin instillation.

*Chronic Vessel Cannulation:* The principal requirement of easy and repeated access to the patient's circulation was met by surgically cannulating an artery and a vein (usually the radial artery and the antecubital vein) shortly after admission to the Center. The tapered plastic cannulae remained in place between dialyses, sealed by a short, closed tygon tube or by a threaded nylon fitting with a stopcock through which heparinized saline was instilled at hourly intervals (figure 5). The cannulae were taped to the patient's extremity to permit unencumbered ambulation. Patients were under constant surveillance by members of the enlisted technician-team while the cannulae remained in place.

*Regional Heparinization:* In patients with recent bleeding or fresh wounds, only the extracorporeal blood circuit was heparinized.<sup>13, 30</sup> Syringe



driver pumps \* were used to infuse calculated † amounts of heparin and protamine through the stopcocks of the arterial and venous cannulae, respectively, to prevent clotting in the dialyzer and to keep the patient's blood clotting time normal (figure 6). At first, heparin concentrations were monitored by a modified thrombin titration<sup>31</sup> technic, but more recently, single-tube clotting times, determined on samples aspirated through a rubber cuff on the arterial cannula proximal to the heparin infusion (via the stopcock), have proved to be much simpler, and satisfactorily accurate.

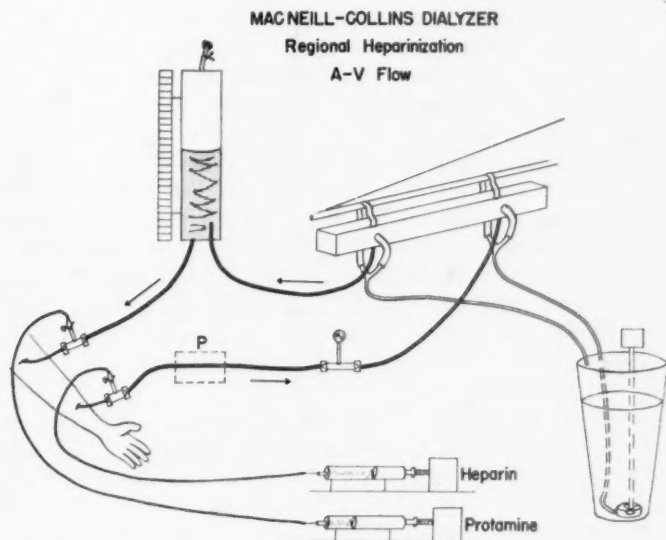


FIG. 6. Extracorporeal circuit with regional heparinization, artery-to-vein flow. If blood flow is too slow, a blood pump may be incorporated at P. The manometer reads perfusion pressure, which rises if clotting occurs in the dialyzer or venous obstruction occurs.

Standard clinical laboratory methods were used for chemical, hematologic and bacteriologic determinations. Blood for chemical determinations was drawn in the morning; the resulting nonprotein nitrogen and potassium concentrations therefore represent peak values on days when dialysis was performed.

### RESULTS

*Technical:* The enlisted technicians developed great skill in assembling dialyzers and circuits and in operating them, in performing the dialyses, in mixing and changing dialysates, and in performing and monitoring

\* Most recently, we have used Dual Infusion/Withdrawal Pumps, Model 600-910, Harvard Apparatus Company, Inc., Dover, Massachusetts.

† See Appendix for sample calculation.

regional heparinization and related technical details, under the direct supervision of the physicians and nurses of the Renal Center Staff.

The average nonprotein nitrogen and potassium levels ( $\pm$  one standard deviation) recorded in figure 2 indicate the high degree of chemical control afforded by this procedure. Wide and sudden fluctuations in extracellular osmolality and pH—as, for example, those often brought about by conventional dialysis—were avoided. Such control was more difficult in those patients whose renal failure followed severe trauma, but was ultimately established in them and maintained despite prolonged oliguria.

Single-channel cannulae were usually placed initially in the radial artery and antecubital vein. Anterior tibial arteries were also used, as well as a variety of other superficial veins. The cannulae delivered and accepted an adequate blood flow (75–250 ml./min); among arteries for an approximate average of 10 days (range, from one to 22 days) each, while the average life of a single-channel venous cannula was about seven days (range, from one to 20 days). Averages of 6.1 and 4.3 dialyses were served by the arterial and venous cannulae, respectively. When these cannulae became nonfunctional, surgical cannulation of further vessels, or of the same vessel at a different site, was undertaken. In addition, multichannel cannulae\* were also used, and these were usually functioning and not associated with thrombi after from one to three weeks' use. Insertion of the cannulae on the day prior to dialysis prevented oozing from cutdowns during dialysis, even under total heparinization.

Cultures from the lumen of the sealed cannulae sometimes revealed growth of organisms within a few days of the insertion. The organism recovered in such instances was usually an *Aerobacter-Klebsiella*, suggesting that contamination may have occurred in the process of handling the cannulae. Despite various technical maneuvers designed to eliminate this problem, most—but not all—dialyses in most of these patients were associated with a 30- to 60-minute shaking chill, beginning from 30 to 60 minutes after the start of dialysis, frequently with a rise in temperature, and a blood culture positive for *Aerobacter-Klebsiella*, *Pseudomonas aeruginosa*, *Escherichia coli*, or *Staphylococcus aureus*. This bacteremia abruptly disappeared in the majority of instances; patients usually retained breakfast, and ate the midday meal (both served during dialysis) without further untoward effect. The number of organisms so introduced was apparently small, but it is nevertheless noteworthy that these patients suffered no apparent ill effect from these recurrent and threatening episodes.

Regional heparinization was performed in 66 of these dialyses. With the mechanical pump (see footnote, page 999) the procedure was simple, automatic and free of difficulty. Measured heparin levels usually approximated 10  $\mu$ g./ml. or more in the dialyzer, and zero in the patient. Clotting times were normal, or were brought to normal by giving additional prota-

\* Fabricated by Cordis Corporation, 241 Northeast 36th Street, Miami 37, Florida.

mine sulfate intravenously. Although an occasional dialyzer clotted, this occurred no more frequently with regional than with general heparinization, and was rare in either circumstance. No discernible untoward effect resulted from the administration of as much as 550 mg. of heparin and 750 mg. of protamine daily over many days. With these methods, actual or impending hemorrhage seems to be effectively eliminated as a contraindication to hemodialysis.

*Clinical Findings. Mental and Neuromuscular State, Ambulation:* In general, the typical agitated depression, lethargy, drowsiness and twitching of uremia were either absent or barely detectable on admission, nor did these signs appear in the subsequent clinical course. As a rule, these patients remained alert and cooperative (figure 7). No hallucinations, convulsions or abnormalities in behavior occurred, with the exception of case 8, who developed typical (and unexplained) catatonia on her twelfth and thirteenth post-onset days, which vanished as suddenly as it appeared; and of case 10, whose relentlessly downward course to coma and death could be attributed to the extensive intracerebral hemorrhage and necrosis found at autopsy. It is noteworthy that abnormal behavior during oliguria and early diuresis did not occur, although it might have been expected in several instances: case 1 had been hospitalized for schizophrenia, was released one month prior to onset of acute renal failure, and only in the late diuretic phase required further psychiatric treatment; case 4 had stabbed himself; case 5 drank carbon tetrachloride in a suicide attempt; case 6 had attempted a criminal abortion.

These patients played cards, read, watched television, and maintained a sense of humor and an interest in the dialysis procedure, the ward routine and other patients. Cases 5, 7, 10, 11 and 12 were confined to bed largely because of injuries, and acute glomerulonephritis indicated bed-rest for case 15. After from six to eight weeks of oliguria, the patients with renal cortical necrosis preferred to stay in bed and complained of weakness. The remaining patients were able to ambulate between dialyses, despite continuing oliguria. Clinical crises, previously so common, especially at night, occurred only rarely in some patients and not at all in others.

However, on close observation after one or more dialyses, or on comparison of color-sound motion picture films documenting a series of clinical interviews, alert patients became even more alert after one or more dialyses, and subtle neuromuscular hyperactivity disappeared. In tests involving simple mental arithmetic (e.g., serial subtraction of seven from 100), seemingly alert patients were often unable to perform normally. Until tested, the patients themselves were apparently unaware of any such incapacity; they were usually surprised, and in one instance alarmed, at the discovery. This deficit persisted even in alert patients, but gradually improved during oliguria, presumably by virtue of practice, the effects of dialysis, general clinical improvement, or a combination of these.



FIG. 7. Patients treated with prophylactic hemodialysis are shown on various days following onset of acute renal failure. *A.* Case 4, 14th day. *B.* Case 7, 18th day. *C.* Case 9, 27th day. *D.* Case 11, 21st day. *E.* Case 13, 48th day. *F.* Case 14, 86th day.

*Appetite, Thirst, Diet, Gastrointestinal Function:* In general, patients having anorexia, nausea or marked thirst on admission experienced a return of appetite and less thirst following successive dialyses. Vomiting had occurred at least once prior to admission in most patients, in spite of low levels of azotemia, perhaps partly as an effect of the inciting episode; other patients did not vomit at all. Because unutilized metabolites could be removed by dialysis as they accumulated, patients were permitted an unrestricted selection from the hospital menu; between-meal feedings were encouraged. Protein-free, low-potassium carbohydrate-fat mixtures were specifically avoided, in the belief that a balanced diet would be needed to supply essential nutrients which might be depleted by dialysis. The estimated daily food intake provided between 1,000 and 3,500 calories and between 30 and 75 gm. of protein. Parenteral feeding was unnecessary except in case 5 (jaundice and vomiting due to hepatic injury), case 10 (progressive coma), and case 11 (during resolution of postsurgical ileus). Fluid intake could frequently be liberalized by means of ultrafiltration with dialysis, and this technic was used more often when patients stated that they could eat more solid food if they had more fluid to drink. Vomiting also occasionally occurred in several patients later in the clinical course, e.g., with dialysis during episodes of chills, and (in case 7) prior to amputation of the lower leg, rendered necrotic by failure of a popliteal arterial graft. Diet was modified and partly limited by the gastrectomy and recurrent bouts of partial intestinal obstruction in case 11.

Mouth care, including brushing the teeth, irrigating all corners of the mouth, inspecting teeth and gums for adherent material, oil or ointment application to lips, every two to four hours, seemed decisive in avoiding or healing oral lesions in patients so treated. Improved nutrition and increased fluid intake may have contributed. Nevertheless, suppurative parotitis complicated the course in cases 5 and 6. Bowel function in most patients was normal except, as expected, in the first few post-onset days. Diarrhea of undetermined etiology occurred in case 14 in the latter weeks of hospitalization. Melena, hematemesis and "uremic colitis" did not occur.

*Body Weight Changes:* Despite the improved nutrition and high vitamin intake in these patients, weight loss was the rule. As expected, it proceeded more rapidly in the patients with continuing infection and tissue necrosis (e.g., an average of 0.4 to 0.6 Kg./day during oliguria in cases 7 and 11) than in the nontraumatized patients or those without residual, unhealed wounds (average, 0.12; range, 0.0 to 0.26 Kg./day). Associated liver injury may have favored the weight loss in case 5 (average, 0.26 Kg./day). Weight loss did not seem greater than could be reasonably anticipated in patients without renal failure hospitalized for similar illness or injury.

*Resistance to Infection; Wound-healing:* Both survivors and fatalities were conspicuously free of significant infection. "Uremic pneumonitis" did not occur. The tissue of the midportion of the epigastric laparotomy

wound in case 11 (figure 8) was injured in the initial shotgun blast. Necrosis with infection resulted in a slow dehiscence of this part of the incision. However, the underlying intestine became adherent, and infection subsided. Stab wounds through which drains had extended into the pancreatic bed continued to drain purulent material, but these became shallower; by the time of discharge, on the seventieth hospital day, they had become narrow channels extending 3 to 4 cm. into the abdomen. Generalized peritonitis did not occur. The episodes of bacteremia during dialysis appeared to be self-limited, and did not progress to the clinical picture of septicemia. Except for aspiration pneumonia in case 12, the three patients with acute tubular necrosis and the two with bilateral renal cortical necrosis who died were free of infection at autopsy. Cutdown wounds rarely became

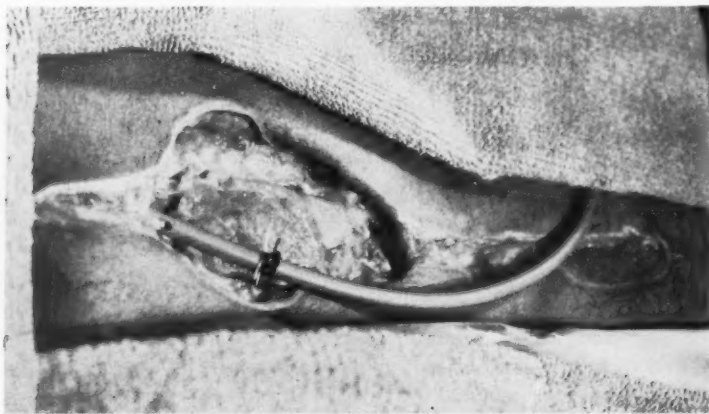


FIG. 8. Laparotomy wound, case 11, 19th post-onset day during oliguria. Note evidence of healing and granulation-tissue formation despite dehiscence of midportion.

infected, even those performed on cases 13 and 14 after 10 or more weeks of oliguria. Like other wounds in these patients, they also healed well. The wound in figure 8 (nineteenth post-onset day) shows clear evidence of healing and of granulation tissue formation, despite the fact that urinary output had averaged 72 ml. per day for the preceding 15 days, and that the patient would excrete 1,000 ml. in 24 hours for the first time nine days later. The thoracotomy wound in case 4 is also shown (figure 9) 16 days following onset of renal failure with oliguria lasting 13 days. Wounds of amputation (case 7) and fasciotomy for relief of pressure of a hematoma (case 5) also healed well.

*Hematology and Bleeding:* During the first seven to 10 days of the oliguric phase, all of these patients became anemic, with individual hematocrits ranging as low (on one day) as 12%. Return toward normal occurred in late diuresis, the lowest hematocrit values being recorded in



early diuresis. Anemia persisted despite the transfusion of 200 to 300 ml. of blood at the end of most dialyses. These transfusions consisted of the sedimented erythrocytes left over from priming the dialyzer circuit, and the blood which would flow spontaneously from the dialyzer and circuit. Studies of erythrocyte survival were not attempted because of frequent dialysis and transfusion; however, supernatant plasma of postdialysis samples revealed hemolysis on only one occasion. Figure 10 depicts the mean and range of hematocrit and reticulocyte counts in these patients in oliguria, before the "day of diuresis" and after it. Reticulocyte counts were generally highest when hematocrit and hemoglobin levels were lowest, and occasionally



FIG. 9. Healed thoracotomy wound, 16th post-onset day in case 4.

reached high levels, e.g., 9.6, 7.7, 8.0 and 7.2% in cases 2, 5, 7 and 13, respectively.

When dialysis was performed several hours after cannulation, bleeding from cutdown sites did not occur, even under general heparinization. This may have been a factor in the subsequent improved healing of these wounds. A spontaneous hemorrhage into the muscle and fascial spaces of the thigh occurred in case 5 despite regional heparinization. This was thought to follow a femoral venipuncture, but fasciotomy with exploration showed that the hematoma did not extend to the inguinal region; the exact explanation for the hemorrhage remains in doubt. The intracerebral hemorrhage in case 10 occurred despite adequately controlled regional heparinization;

whether the dialysis procedures accelerated bleeding is not known. No other significant bleeding occurred. In the treatment of case 15, complement and globulin-free blood was used to fill the dialyzer and for other transfusions on all but one occasion. Washed, compatible erythrocytes were suspended in 5% human albumin in saline. This technic presumably avoided the transfusion of globulin and complement which could possibly continue or augment glomerular injury, as suggested by Schreiner.<sup>32</sup>

*Mortality:* Cases 8, 10 and 12 with acute tubular necrosis died during oliguria of 26, 11 and seven days' duration, respectively. Autopsy was unrevealing in case 8, but revealed lesions adequate to explain the deaths of cases 10 and 12 (table 2). The portions of the right kidney in case 12 not involved in infarction revealed evidence of tubular necrosis. Cases 13 and 14 had complete atrophy of renal cortices after 73 and 92 days of oliguria, respectively. Both rapidly developed severe and unexplained metabolic acidosis prior to death, and died in shock unresponsive to adrenal steroids, vasopressors, etc. The autopsies failed to reveal obvious causes of death. The anterior pituitary in case 13 was necrotic, but this lesion was not found in case 14. Tissues were grossly in good condition.

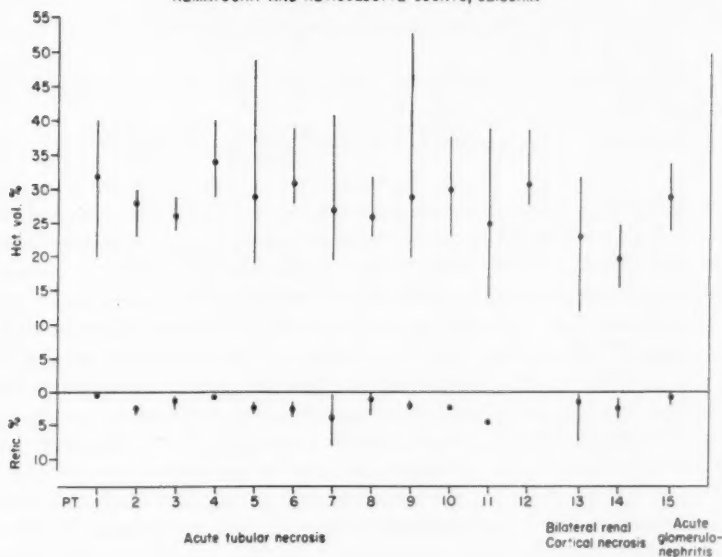
#### DISCUSSION

The basis of this investigation is the conviction that the sickness of uremia may be caused in some way by a retention of dialyzable substances which interfere with the function of many cells and tissues. The clinical course of such sick uremic patients often suggests that, beyond a point, such potentially reversible chemical derangement may begin to do some fundamental damage which is no longer reversible by dialysis, and which is manifested clinically by such apparently irreversible phenomena as collapse of resistance to infection, progressive wasting, and failure of wound healing. Since certain of the manifestations of acute uremia in patients with acute renal failure such as nausea, vomiting and drowsiness, could be readily reversed by dialysis, the *prophylactic* use of dialysis, before clinical or chemical derangements became marked, might be expected to prevent other, often lethal complications as well. Our experience with the first 15 patients so treated seems to support this hypothesis. The principal results may be summarized as follows:

1. Marked azotemia, hyperkalemia and other distortions of the plasma chemical pattern were readily controlled or prevented.
2. The common symptoms of clinical uremia—anorexia, nausea, vomiting, drowsiness, coma, staring, twitching and convulsions—were virtually eliminated.
3. Infection, including that presumably introduced in consequence of chronic vessel cannulation, appeared to subside readily, without evidence of residual injury.

# PROPHYLACTIC HEMODIALYSIS

HEMATOCRIT AND RETICULOCYTE COUNTS, OLIGURIA



# PROPHYLACTIC HEMODIALYSIS

HEMATOCRIT AND RETICULOCYTE COUNTS, DIURESIS

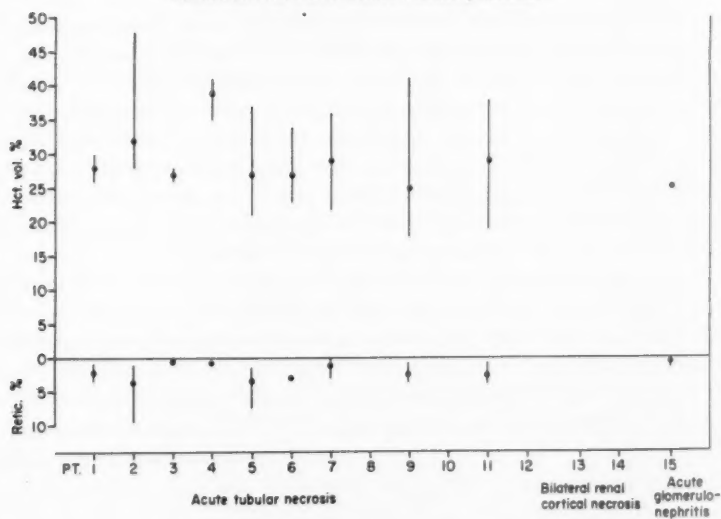


FIG. 10. Hematocrit levels and reticulocyte counts in 15 patients with acute renal failure treated with prophylactic hemodialysis. Points represent the means and vertical bars the ranges of values obtained in these patients during oliguria (above) and diuresis (below).

4. Healing of cutdown sites and other wounds resembled that in patients without acute renal failure.
5. Unrestricted food intake and ambulation seemed to favor convalescence from the inciting injury or illness.
6. Significant reticulocytosis was encountered in oliguria and early diuresis.

Other findings usually associated with symptomatic acute renal failure remained in some or all of these patients, despite their obvious general clinical health: (1) subtle deficits in certain mental processes persisted, though with improvement, in patients who seemed otherwise alert; (2) a loss in body weight continued at varying rates into late diuresis, despite the improved food intake; and (3) anemia occurred in spite of reticulocytosis, commonly reaching hemoglobin levels of 7 gm.% (hematocrit levels of 20%) in late oliguria and early diuresis. In addition, transient bacteremia with fever and chills occurred in some patients within an hour of the beginning of dialysis, possibly because of contamination of the indwelling cannulae. During this treatment, three patients with presumably reversible acute tubular necrosis died in oliguria, of intercurrent or underlying significant disease. The persistence of these abnormalities suggests that not all of the manifestations of uremia are directly related to toxic substances which are dialyzable through cellophane. Thus it may be that a hemolytic process continues to contribute to the anemia of uremia<sup>33, 34</sup> and remains decisive even though a reticulocytosis occurs which indicates at least a partial release of bone marrow suppression. Persisting subtle mental deficits in alert patients, like the continuous loss of body weight, may indicate variable sensitivity of the brain or of anabolic processes in many tissues to the several chemical abnormalities of uremia. In any event, this experience obviously forms an insufficient basis for any final statement at this time; however, as indicated in the introduction, the repeated, generally stable or "uphill" clinical course of these patients contrasts markedly with our past experience in treating patients with acute renal failure, either without dialysis, or with dialysis on conventional indications.

The concept of prophylactic dialysis may be considered to be a logical extrapolation of the observations and recommendations of Anthonisen,<sup>23</sup> Salisbury,<sup>14</sup> Scribner<sup>35</sup> and others, that a smoother clinical course and better prognosis are apparent consequences of "earlier" dialysis, namely, the application of dialysis before the patients are severely uremic or preterminal; dialysis is usually useless as a "last resort."<sup>10, 16, 20</sup> Similar findings were reported by Houck<sup>36</sup> in terms of fewer uremic symptoms and longer survival in bilaterally nephrectomized dogs when dialysis was begun within 20 hours of surgery, and performed three times daily in the first week and twice daily thereafter. Scribner has also recently reported his initial experiences with *continuous* dialysis,<sup>37</sup> by which patients are connected to the dialyzer

throughout each 24-hour period through the beginning of diuresis. This technic appears to be a further extension of the hypothesis and the technics invoked in the present study. In our opinion, continuous dialysis, like the foregoing technics, should receive more extensive application to determine whether further advantages accrue to patients so treated.

While there is increasing recognition of the value of earlier dialysis, the *published* consensus, and the practice in many centers at present, is still to apply dialysis to relatively ill rather than to relatively healthy patients. This is implied by the usually quoted indications for dialysis, namely, definite or progressive clinical uremic illness and/or progressive potassium intoxication, occurring despite careful suppressive therapy.<sup>7-15</sup> In many of these reports, the recorded, relatively high predialysis levels of azotemia<sup>11, 38</sup> clearly indicate the extent of chemical deterioration (and, inferentially, of clinical deterioration) which is imposed by the conventional indications for dialysis.

Certain effects of such conventional dialysis have been suggested, particularly in acute renal failure following trauma. Some reduction in mortality may be achieved, but this is not conclusively demonstrated;<sup>20</sup> all series include patients who could not possibly have survived without dialysis treatment.<sup>15, 39</sup> The clinical course may be smoother. Fatalities live longer, and a larger percentage of them therefore tend to die in diuresis rather than in oliguria. But when death due to potassium intoxication is avoided, other complications and apparent causes of death, such as sepsis, wasting and impaired wound healing, seem to occur more frequently.

Opinion persists, however, that acute renal failure is essentially a benign disease, responsive to careful medical management in the absence of complications.<sup>7-9</sup> With such management, it is estimated that both morbidity and mortality should be very low and, in the absence of "lethal complications," should approach zero.<sup>9</sup> The data in table 1, from centers where dialysis is readily available and frequently performed, belie these confident assertions. The reasons for this remarkable divergence between data and opinion are also pertinent to whether the results of prophylactic hemodialysis constitute a real contrast with, and improvement over, past experience. This judgment for each physician will depend largely on his own past experience and appreciation of clinical acute renal failure. The issue is extremely difficult to resolve objectively because (1) no two physicians are likely to see the same proportion of patients with "uncomplicated" acute renal failure; (2) there is a wide variation in severity between patients and between etiologic groups,<sup>7-9, 20</sup> and hence between physicians' personal impressions of the disease; (3) most large series of carefully studied patients come from centers to which they have been referred as possible candidates for dialysis; (4) similar data are not available on patients not so referred; and (5) some physicians tend to eliminate from mortality statistics and their evaluation those patients with acute renal failure who die of severe complications which developed during the clinical course, or those in whom diuresis

has not occurred prior to death three to four weeks following onset, i.e., supposed instances of "irreversible renal injury." Certainly, mortality will continue to occur regardless of treatment in all series from such undiscovered, unremedied or irremediable situations as a ligated common bile duct, mesenteric artery thrombosis with infarction of the bowel, generalized peritonitis, intercurrent myocardial infarction, massive pulmonary embolus, cerebral vascular accidents, etc. However, one must ask what part the uremic state might have played in such events. Mortality statistics "corrected" by eliminating such patients, as Bluemle has stated, "ignore the detrimental influence which uremia may exert on the patient's potential for recovery from any illness or complication. They further tend to give a false basis for evaluating prognosis in any given case."<sup>20</sup> In any event, it is difficult to explain the relatively high frequency of wasting or generalized sepsis (due to organisms which normally inhabit the skin, or the gastrointestinal or respiratory tracts) in patients whose renal failure follows nephrotoxic poisoning, hemolytic transfusion reaction or obstetric accidents. On the face of it, little in these etiologic settings seems to justify the incidence of complications, and the recorded 25 to 40% mortality which occurs at least among patients at Renal Centers who develop conventional indications for dialysis. In other words, "uncomplicated" acute renal failure with its favorable prognosis may be relatively uncommon. Conversely, perhaps some of the "complications" are properly a part of the uremic syndrome, which may be preventable but not treatable by dialysis; our hypothesis is partly based on this intriguing idea.

Further objection to prophylactic dialysis may be based on the occurrence in all series of survivors even from prolonged oliguria or from severe post-traumatic renal insufficiency after many dialyses on conventional indications.<sup>19,20</sup> It should be noted, however, that such survivors tend to be the exception rather than the rule; one objective of prophylactic dialysis is to establish the reverse situation as the norm for these patients.

Again, objection to dialysis of any sort is often raised in the case of the mild instance of acute renal failure in which the patient accumulates nitrogen and potassium very slowly, maintains a moderate oliguria of 150 to 300 ml./24 hours, enters into diuresis in less than two weeks, and experiences only lethargy, nausea and vomiting. Certainly, dialysis hardly seems indicated in such instances. However, it should be noted that this situation may be relatively uncommon (as it is in our experience), and that the description is *retrospective*. It is most difficult—if not impossible—to *predict* such a mild course for any patient. Generally the smoothness of the clinical course and the fact of survival are known only at the end of the clinical course, and not at the beginning. In contrast, we have been impressed by the number of patients with nephrotoxic injuries, obstetric accidents or transfusion reactions who "should have had" a benign course but who died, often in the diuretic phase, even after oliguria of relatively



short duration. A related example is given by Salisbury<sup>14</sup> in analyzing which of the previous patients in his series might have received dialysis treatment under a new policy of earlier dialysis. He found six patients who would have received dialysis treatment under the new criteria, but who in fact recovered without the use of the artificial kidney, and he concluded that "this treatment would have been superfluous." We would urge that dialyses applied to patients who might otherwise survive should not under any circumstances be considered to be superfluous. Rather, the judgment of whether to undertake dialysis should also be made in view of possible risks in *not* employing this procedure. We would question both the wisdom and the safety of subjecting patients to several days of avoidable nausea, vomiting, drowsiness and thirst, which not only implies significant discomfort to the patient but may also impose considerable risk of aspiration, pneumonia and other unexpected "complications."<sup>7, 16</sup>

At present we suggest that hemodialysis should be applied prophylactically in patients with acute renal failure before the nonprotein nitrogen reaches 150 mg.% (blood urea nitrogen, 120 mg.%), however mild the clinical course may seem. This arbitrary choice of a level of azotemia does not imply that it is the figure of choice, or that the toxic substance(s) mentioned in the hypothesis is measured by or necessarily varies with non-protein nitrogen concentration; subsequent experience may show that prophylactic dialysis is better applied at lower or higher levels of nonprotein nitrogen or other chemical parameter. With regional heparinization, there are no known contraindications to this technic. Present requirements for the procedure include at least one trained technician or nurse for each dialysis to be performed at any one time, operating under a trained physician's direction. While it is obviously wise for a physician to supervise the start of dialysis when the circuit is connected to the patient and blood flow is begun, he is not otherwise needed, in most instances, for the technical conduct of these procedures. His function is rather to stand by for necessary clinical decisions or for possible emergencies.

Any dialyzer may be used for this technic. It seems obvious, however, that instruments featuring a low cost per dialysis and a small requirement for banked blood would be particularly advantageous for frequent or daily use. In our hands, the MacNeill-Collins dialyzer has been found to satisfy these requirements.

Furthermore, this technic is applicable to small children, as demonstrated by case 15, who was four years old. It is also possible that peritoneal dialysis<sup>8, 40</sup> might be used prophylactically. More experience is needed, however, before its application can be defined in patients with post-traumatic renal insufficiency, with and without recent abdominal wounding or surgery.

It is evident that frequent dialysis implies an organized, disciplined and well supported team of trained physicians, nurses and technicians. Even more important is the executive resolve to carry out management, including

dialysis, on a systematic, routine basis, without allowing inertia in the face of a somewhat complex dialysis procedure to result in procrastination and delay. The relative rarity of these patients suggests that prophylactic dialysis should not be attempted in every hospital. Rather, as Strauss<sup>9</sup> has suggested, the patients should be concentrated at Renal Centers serving populations of several millions each; adequate financing and communication should be sought for them. Such concentration affords the further priceless opportunity for careful clinical study and investigation of this disease, and hence for improving treatment further. Certainly, without a concentration of patients there can be no such opportunity.

#### SUMMARY

Prophylactic hemodialysis has been employed in the treatment of 15 patients with acute renal failure due to acute tubular necrosis (12), bilateral renal cortical necrosis (two), and poststreptococcal glomerulonephritis (one). Dialyses, usually lasting six hours each, were begun before clinical evidence of uremia developed in each patient and/or before the nonprotein nitrogen reached 200 mg.%, and were repeated daily or often enough to maintain the nonprotein nitrogen below 150 mg.%. The hypothesis underlying this technic postulates (1) that wasting, sepsis and impaired wound healing in these patients may reflect tissue injury by the same dialyzable toxic agents which produce the uremic symptoms that are readily reversible by dialysis, and (2) that repeated dialyses should therefore prevent both clinical uremia and the later, often lethal sequelae.

The results contrast dramatically with our own past experience in treating patients with acute renal failure with a carefully executed medical regimen together with hemodialysis on conventional indications. Except in one instance of crush injury with progressive intracerebral damage, and one brief occasion in another individual, these patients experienced a stable, convalescent clinical course, remained free of uremic symptoms or chemical imbalances, ate at least three meals daily which were unrestricted in amount and composition, and were ambulatory between dialyses unless confined to bed by associated disease. Wounds healed well. Infection either did not occur, or subsided after appropriate therapy. Fluid restriction was liberalized by means of ultrafiltration with dialysis. Regional heparinization of only the extracorporeal circuit eliminated actual or impending bleeding as a contraindication to dialysis. Chronic vessel cannulation made the frequent dialyses possible, but may have provided the route for repeated, transient bacterial contamination of the blood stream in the first hour of many dialyses. Marked anemia, despite reticulocytosis, moderate to mild weight loss and some mental deficit persisted in spite of the general clinical improvement and well-being. Three patients with tubular necrosis died after seven, 11 and 26 days of oliguria; both patients with bilateral renal cortical necrosis also succumbed, on the seventy-third and ninety-second days

of renal failure, and after 29 and 40 dialyses, respectively. At autopsy, evidence of sepsis was conspicuously absent. The remaining 10 patients survived. Thus some, but not all, clinical manifestations of acute renal failure appear to be favorably influenced by prophylactic dialysis treatment.

Our initial experience in this group of 15 patients does not of course prove that freedom from complications and a significantly better outlook for survival can be assured to patients with acute renal failure by these methods. However, it seems to offer a reasonable hope of this possibility which we cannot attach to management by medical measures alone, or by dialysis on conventional indications. If this hope is realized in greatly extended, subsequent series, then it seems inevitable that some form of prophylactic dialysis, or some equally effective alternative, should be adopted in treating the majority of patients with acute renal failure.

#### APPENDIX

##### Regional Heparinization: Sample Calculation of Heparin and Protamine Dilutions

##### 1. Heparin

Anticipated extracorporeal blood flow rate = 150 ml./min.

Desired extracorporeal blood heparin concentration = 10  $\mu$ g./ml.

$150 \times 10 = 1,500 \mu\text{g./min.}$  or 1.5 mg. heparin/min.

Position 7 on Infusion Pump with 50 ml. syringe delivers 0.382 ml./min.

$\frac{1.5 \text{ mg./min.}}{0.382 \text{ ml./min.}} = 3.93 \text{ mg./ml.}$  desired final heparin concentration

(10 mg./ml.)\* (X ml.) = (3.93 mg./ml.) (50 ml.)†

X = 19.6 ml. of commercial heparin, qs. ad. 50 ml. in the syringe with sterile, isotonic saline.

##### 2. Protamine

Assume a protamine  $\text{SO}_4$  requirement of 1.33 mg./mg. of heparin.

$\therefore 19.6 \text{ ml. (196 mg.)}$  of heparin require  $1.33 \times 19.6 = 261 \text{ mg.}$  or 26.1 ml. of protamine (also at 10 mg./ml. concentration) for neutralization. This is also diluted qs. ad. 50 ml. in the syringe with sterile, isotonic saline.

#### SUMMARY IN INTERLINGUA

Hemodialyse prophylactic esseva usate in le tractamento de 15 patientes con acute disfallimento renal. Le causa del disfallimento esseva acute necrose tubular in 12 del casos, bilateral necrose reno-cortical in duo, e glomerulonephritis post-streptococcal in un. Le dialyses, usualmente de un duration de sex horas cata un, esseva initiate ante le disveloppamento de manifestationes clinic de uremia e/o ante que le nivello de nitrogeno non ligate a proteina attingeva 200 mg%. Illos esseva

\* Concentration of commercial heparin.

† Volume of syringe to be used.

repetite omne die o satis frequentemente pro mantener le nitrogeno non proteinic a infra 150 mg%. In summa, 193 dialyses esseva executate in iste gruppo de patientes in le curso de un total de 398 dies de oliguria. Le theoria al base de iste technica insiste (1) que le perdita de peso, le sepe, e le imperfecte coalescentia de vulneres in iste patientes reflecte possibilmente un injuria tissular per le mesme dialysabile agentes toxic que etiam produce le symptomata uremic le quales se revertit facilmente sub le effecto del dialyse e (2) que repetitive dialyses deberea per consequente prevenir tanto le uremia clinic como etiam—plus tarde—le sequellas que es frequentemente de character letal.

Le resultados in le hic-presentate serie contrasta marcatamente con nostre proprie experientias passate in le tractamento de patientes con acute disfallimento renal per medio de un meticulosemente observate regime medical, con hemodialyse solmente super le base del indicationes conventional. Con le exception de un sol caso de vulneres contusional con progressive lesiones intracerebral (e un breve episodio in un secunde caso), iste patientes experienciava un stabile curso de convalescentia clinic; illes remaneva libere de symptomata uremic o de disequilibrio chimic; illes mangiava al minus tres repastos per die, le quales esseva sin restriction in quantitate e in composition; e illes esseva ambulatori durante le intervallos inter le dialyses excepte in tanto que associate morbos requireva lor allectamento. Le vulneres se coalesceva ben. Infectiones non esseva frequente e, in tanto que tales occurreva, illos subsideva post le appropriate therapia. Le restriction de liquido esseva liberalisate per medio de ultrafiltration con dialyse. Heparinisation regional de solmente le circuito extracorporee esseva effectuate in 66 del dialyses e pareva eliminar sanguination effective o imminente como contraindication contra le institution de dialyse. Chronic cannulation vascular rendeva possibile le frequente repetition del dialyses sed representava possibilmente le via de invasion pro le repetitive transiente contamination bacterial del circulation de sanguine durante le prime hora de multes del dialyses. Cannulas arterial—usualmente in le arteria radial—remaneva functional durante un periodo medie de 10 dies, durante que le vita medie del cannulas venose a canal unic esseva circa septe dies. Marcate anemia in despecto de reticulocytosis, moderate o leve formas de perdita de peso, e un certe deficit mental persisteva in despecto del melioration clinic general e del senso de ben-esser subjective. Tres patientes con necrosis tubular moriva post septe, 11, e 26 dies de oliguria. Etiam le duo patientes con bilateral necrosis cortico-renal moriva, le un le septanta-tertie e le altere le novanta-secunde die de disfallimento renal, post 29 e post 40 dialyses, respectivamente. Al necropsia, evidencia de sepe esseva conspicueamente absente. Le remanente 10 patientes superviveva. Assi certe manifestationes clinic de acute disfallimento renal—ben que non omnes—pare esser influentiate favorabilemente per un tractamento de dialyse prophylactic.

Nostre experientia initial, evidentemente, non pote supportar le conclusion que le methodos usate es capace a garantir al patiente con acute disfallimento renal le exclusion complete de complicationes e un significativamente meliorate prospecto a superviver. Tamen, un certe spero con respecto a ille possibilitate es justificata, i.e. un spero que non es inspirate per un regime de mesuras exclusiveamente medical o de dialyse super le base del indicationes conventional. Si iste optimismo es justificata per multo plus extense series de casos futur, allora il pare inevitabile que le un o le altere forma de dialyse prophylactic (o un equalmente efficace alternativa) debe esser adoptate in tractar le majoritate del patientes con acute disfallimento renal.

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## CASE REPORTS

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### MALABSORPTION SYNDROME DUE TO AMYLOIDOSIS OF THE INTESTINE SECONDARY TO LEPROMATOUS LEPROSY: REPORT OF A CASE \*

By R. M. BEDDOW, M.D., and I. L. TILDEN, M.D., *Honolulu, Hawaii*

AMYLOIDOSIS is usually classified as follows: (1) primary, systemic or focal, of unknown etiology; (2) secondary, the end result of some other chronic disease, most notably tuberculosis, but also syphilis, rheumatoid arthritis, osteomyelitis, bronchiectasis, cancer or lepromatous leprosy; and (3) amyloidosis associated with multiple myeloma. Secondary amyloidosis, by far the most common, is said to involve the liver, spleen, kidneys, adrenals and intestine most often; primary amyloidosis, the heart, blood vessels and connective tissues, but there is much overlapping, and some<sup>1</sup> now believe that the separation of cases into primary and secondary types is artificial, and that the differences in the two types are quantitative rather than qualitative. This view has much to recommend it.

Although amyloidosis of the intestine is common, the production of a full-blown malabsorption syndrome due to intestinal amyloidosis is distinctly unusual, and because of this we believe the following case report will be of interest. We wish also to stress the frequency of the occurrence of amyloidosis in lepromatous leprosy, a fact which is little appreciated, judging from reports in the literature.

#### SPRUELIKE SYNDROME DUE TO AMYLOIDOSIS: HISTORICAL ASPECTS

Golden<sup>2</sup> in 1945 reported the case of a 66 year old Negro woman with a long history of gastrointestinal complaints and, more recently, frequent, foul-smelling, light yellow stools associated with abdominal cramps. An upper gastrointestinal series showed narrowing of the antrum and gastric retention. At laparotomy a peculiar, marble-like discoloration of the stomach and intestines was noted. The patient died on the sixty-ninth day following gastric resection, and at necropsy there was heavy amyloid deposition in the stomach and intestine which microscopically was confined chiefly to the muscle coat and muscularis mucosae. The case was classified as primary because no chronic precipitating disease was present.

Adlersberg and Schein<sup>3</sup> in 1947 studied 40 patients with the sprue syndrome; 36 were primary, four secondary. Of the latter, two had amyloidosis of the bowel involving the villi and vessels of the submucosa, one secondary to a malignant renal neoplasm, the other to Hodgkin's disease. In an earlier report,

\* Received for publication May 25, 1959.

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Schein<sup>4</sup> investigated 40 cases of intestinal amyloidosis of both secondary and primary types; many had diarrhea and melena, but only two had the sprue syndrome, possibly the same two mentioned above.

In 1948 Findley and Adams<sup>5</sup> reported the case of a 46 year old male with bulky soft stools, 28% fat by weight, and hypocalcemia. At necropsy, amyloid was deposited in the areolar tissue, blood vessels, spleen, adrenals and intestine, chiefly in the muscularis mucosae and the muscle coat, but some in the villi too. The case was regarded as one of primary amyloidosis.

Dahlin<sup>6</sup> in 1949 noted that Virchow's book (1860) stated that diarrhea may result from enteric amyloidosis, but of the 44 cases in the Mayo series (30 secondary) only one had diarrhea, and no mention is made of the sprue syndrome.

Of the 12 cases reported recently by Bero,<sup>7</sup> five had intrinsic involvement of the gastrointestinal tract, the usual site being the mucosa of the stomach and the villi of the small bowel. Diarrhea was present in two cases and gastrointestinal tract hemorrhage in three, but none showed clinical evidence of sprue.

#### AMYLOIDOSIS IN LEPROSY

Without going into detail regarding the classification of leprosy, we feel that mention should be made that there are two diametrically opposed polar forms of the disease, lepromatous and tuberculoid. In the former there is little natural or acquired resistance to proliferation of *Mycobacterium leprae* in the tissues, bacilli consequently are numerous, the lepromin\* test is negative, and pathologically there is massive proliferation of round or elongated histiocytes in the skin, nerves, testes and, to a lesser extent, the lymph nodes, liver and spleen. In tuberculoid leprosy, on the other hand, a high degree of immunity is present, bacilli are rare and often cannot be demonstrated in the lesions, the lepromin test is positive, and pathologically the hallmark of the disease is the compact, sarcoid-like epithelioid cell tubercle involving the skin, nerves and, rarely, the lymph nodes.

It has been well established<sup>8,9</sup> that in patients with lepromatous leprosy there is an abnormal serum protein pattern consisting of an elevation of the gamma globulin fraction, a decrease in albumin, and a reversal of the A/G ratio. The total proteins may be normal or elevated at first, and later decreased, due to proteinuria, which in turn often results from amyloid involvement of the kidneys. In patients with tuberculoid leprosy, no blood protein changes are present.

Tuberculosis is commonly associated with leprosy, and was a primary or contributing cause of death in 23% of 607 patients dying at the U. S. Public Health Service Hospital in Carville, Louisiana, prior to 1950.<sup>10</sup> Amyloid disease of the kidney, however, was the leading cause of death, and it was thought to result from leprosy rather than tuberculosis. Certainly that is true in Hawaii, where secondary amyloidosis in patients dying of tuberculosis is unknown.

During the 1940's one of us (I. L. T.) received necropsy material from 36 patients with leprosy dying at Kalaupapa, Molokai, and the results as far as amyloidosis and tuberculosis are concerned are summarized in table 1.

\* Lepromin is a suspension in saline solution of boiled, ground-up lepromatous granulation tissue containing many dead bacilli. The test, also known as the Mitsuda reaction, is performed by injecting 0.1 c.c. intradermally. A positive reaction is manifested by the appearance two to three weeks later of an ulcerated nodule at the site of injection.

Seventeen of 36 patients had amyloidosis, and of the 17 there were 15 with the lepromatous type of the disease and two in whom the leprosy was unclassifiable with the data available. There were no cases of the tuberculoid type. These findings are in accord with those of Shuttleworth and Ross,<sup>11</sup> who found that 12 cases in 20 consecutive deaths at Carville had amyloidosis, 10 of which were confirmed by necropsy. In nine of these cases the amyloidosis was responsible for death from renal failure. They also mentioned that amyloidosis was

TABLE 1

Type of Leprosy	Amyloidosis		No Amyloidosis		Total
	With Tbc	No Tbc	With Tbc	No Tbc	
Lepromatous	8	7	5	5	25
Tuberculoid	0	0	0	3	3
Unclassifiable	2	0	2	4	8
Total	10	7	7	12	36

present only in the lepromatous form of the disease, being most common in moderately advanced cases of around two years' duration.

## CASE REPORT

A 30 year old unmarried Japanese male was first hospitalized at Hale Mohalu Hospital, Honolulu, Hawaii, in 1952, with the diagnosis of active lepromatous leprosy. He had first noticed a "rash" near his left ankle, and was seen in the Out-Patient Department of Tripler Army Hospital, where he was treated for a short period of time for dermatitis. However, with the appearance of weakness in the dorsiflexors of the left foot a diagnosis of lepromatous leprosy was made, confirmed by the demonstration of large numbers of acid-fast bacilli in tissue juice from the skin. There was generalized infiltration of the skin of the trunk and extremities by discrete, nodular lesions about the size of a pea, which were red in color and nodular in consistency (figure 1). Discoid plaques were present over the extremities, and the sural nerve was enlarged on the left side, the saphenous nerve on the right. There was slight facial weakness, with a droop of the right corner of the mouth, and widening of the right palpebral fissure.

For the first two years the patient was treated with a sulfone drug, Promin, which was well tolerated, and there was symptomatic improvement. However, in June, 1954, he experienced repeated generalized leprosy reactions, and was no longer able to tolerate any of the sulfones.

The symptoms of the present illness began in July, 1957, at which time the patient complained of anorexia, epigastric pain, occasional attacks of nausea and vomiting, and diarrhea. At this time he was started on an experimental drug (SU-1906 Diphenyl Thiourea Compound—Ciba 15095E), but the gastrointestinal tract symptoms persisted and he was hospitalized at St. Francis Hospital in Honolulu, Hawaii, on August 7, 1957, for gastrointestinal studies. The drug was discontinued. An upper gastrointestinal series at that time was reported as negative except for a questionable area on the lesser curvature of the stomach, suggestive of an ulcer. A urinalysis was negative except for a few leukocytes and red cells per high power field. The erythrocyte count was 4,800,000; hemoglobin, 13.3 gm.; hematocrit, 42%. The white count was elevated to 19,100, with 73% neutrophils and 23% lymphocytes. The



FIG. 1. Photograph taken in 1952 to show extensive nodular infiltration of the trunk and extremities, and large, erythematous plaque of the left lower leg.

patient was discharged on August 9, 1957, on an ulcer regimen, with the diagnosis of acute gastroenteritis and leprosy, lepromatous type, active.

The patient was first seen by one of us (R. M. B.) in December, 1957, because of enlargement of the thyroid which had appeared rather rapidly during administration of the SU-1906. The thyroid was functioning normally, and the moderate, symmetric, nontender enlargement of the gland was thought to be due to the SU-1906, a thiourea derivative. The patient was having six to 10 watery stools daily, and complained of anorexia and epigastric discomfort. His weight—150 pounds—had not changed appreciably since his August admission.

The final admission to St. Francis Hospital was on June 17, 1958, because of persistent severe diarrhea and marked weight loss. Since the last hospitalization, in December, 1957, the patient complained of episodes of frequent, moderately severe epigastric pain, especially localized to the left of the midline. The pain was most severe at night, and was often associated with nausea and vomiting. He continued to have six to 10 watery bowel movements daily, and at times the stools were mushy and yellow in color, with a foul odor. There was no history of dark tarry stools. The patient had lost about 50 pounds of weight during the preceding six months.

Examination revealed severe emaciation, cachexia and asthenia. The skin presented a diffuse, generalized "miliary type" of nodular eruption involving the trunk and extremities. Some of the nodules were brilliantly red in color, while others had a bluish or purplish tint. In addition, there were neurologic manifestations of leprosy consisting of topical anesthesia and hypesthesia in patches distributed over the extremities. The abdomen was slightly distended and tympanitic. Marked tenderness was present in the epigastrium, and a left foot drop was observed. There was slight edema of the ankles.

Initial laboratory studies showed moderate leukocytosis, an elevated sedimentation rate and 4 plus proteinuria, a few hyaline casts, and 100 to 120 erythrocytes per high power field. The blood chemical studies revealed severe hypocalcemia (4.5 mg.%), moderate hypokalemia (3.2 mEq. L.), a normal blood urea nitrogen, and marked hypoproteinemia (3.54 gm.%, with albumin, 2.13 gm.%, and globulin, 1.41 gm.%). The stools contained globules of neutral fat confirmed by Sudan III staining. A flat glucose tolerance curve, a moderately prolonged prothrombin time, and a normal bromsulphalein test were found present.

Proctosigmoidoscopy was performed without difficulty, revealing slight hyperemia of the mucosa, which tended to bleed readily upon contact with the instrument, but the changes were not diagnostic. A chest x-ray was negative, and an upper gastrointestinal series showed a marked disturbance of the mucosal pattern of the duodenum and the remainder of the small bowel, particularly the jejunum. The latter exhibited marked narrowing, and a coarsened, nodular mucosal pattern. The colon showed complete loss of the normal mucosal pattern. The abnormal dilatation or segmentation of the meal in the small bowel seen in idiopathic steatorrhea was not observed. Dr. Richard Moore, the radiologist, felt that these changes were not diagnostic, but that they would be compatible with an extensive inflammatory process involving the small bowel.

The patient was treated as a case of idiopathic steatorrhea, but the response to therapy was unsatisfactory. The prothrombin activity returned to normal, but the total protein remained low (4 gm.%), and there was a lack of significant improvement in the blood chemistry findings. A laparotomy was finally advised after an adequate trial of medical therapy because of the lack of improvement, and because the x-ray findings suggested severe organic changes in the small intestine which might possibly be amenable to alleviation by a surgical procedure.

On July 3, 1958, a laparotomy was performed by Dr. J. E. Strode and a biopsy taken of the jejunum. Surprisingly, both the small and large bowel appeared to be

relatively normal, aside from an unusually pale serosal surface which, on close inspection, had the appearance of a mosaic. When the jejunum was opened the mucous membrane had a somewhat granular appearance. The rest of the abdominal organs appeared to be normal. The biopsy showed extensive amyloidosis, manifested by deposition of amorphous Congo red-positive material in the deeper portions of the lamina propria and in blood vessel walls in the submucosa.

The patient's postoperative course was uneventful, and he seemed to improve subjectively, with disappearance of abdominal pain, lessening of the diarrhea, and return of appetite. He was discharged from the hospital on the ninth postoperative day, July 12, 1958, and returned to Hale Mohalu. However, this improvement was temporary, he failed to gain weight, and within several days his diarrhea returned. His condition slowly deteriorated, and death occurred on August 3, 1958, about one month after the surgical operation.

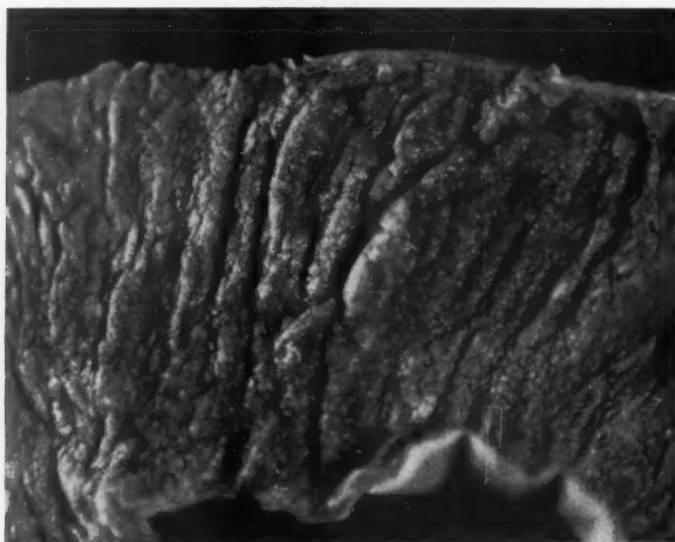


FIG. 2. Close-up view of the jejunum, showing innumerable small mucosal nodules produced by amyloid deposits in the lamina propria.

*Necropsy Findings:* The body was that of a well-developed, emaciated young Japanese male. The only external evidence of leprosy was patchy alopecia of the eyebrows, and the presence of innumerable flat, scaly pigmented macules measuring up to 2 cm. in diameter scattered over the trunk and extremities. There was no infiltration.

The only abnormal finding in the chest was slight enlargement of the heart, and an unusually firm, rigid myocardium.

The liver was moderately enlarged (approximately 1,500 gm.), and had a normal consistency and an unusually dark cut surface.

The kidneys were enlarged, weighing 190 gm. each, and presented a dark, hemorrhagic, "flea-bitten" external surface. Upon sectioning, the pyramids were dark in color, and both cortex and medulla showed many small hemorrhages. The consistency was normal.



The spleen was of normal size (120 gm.), and showed a uniformly dark hemorrhagic cut surface and a very firm consistency. No nodules could be seen.

The stomach was dilated, and both the stomach and the intestine in its entirety presented a flat, atrophic-appearing mucous membrane, with areas of hemorrhage

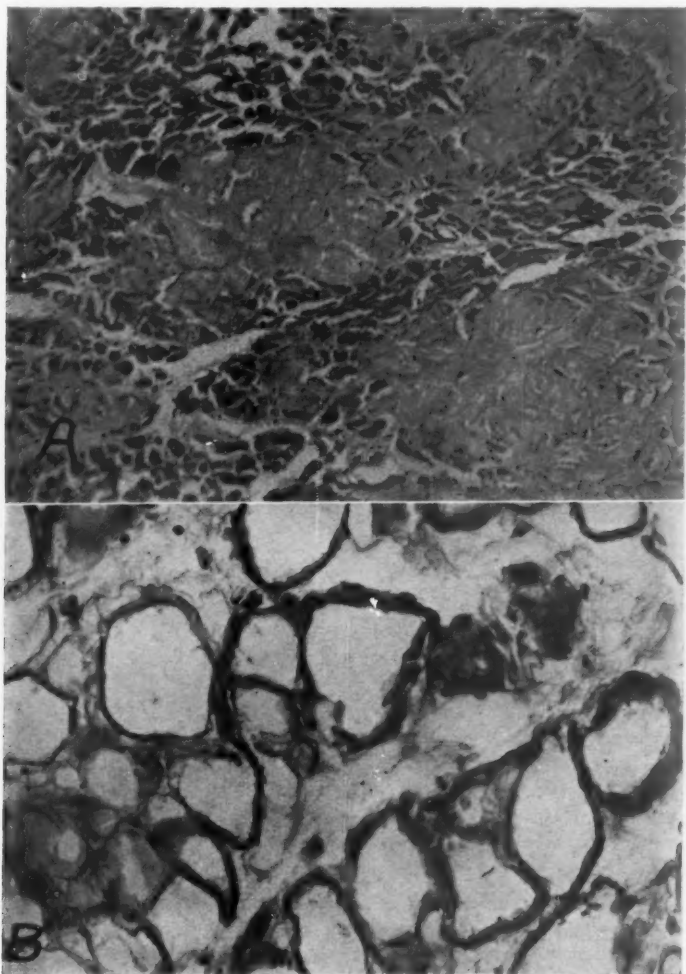


FIG. 3. A. Heavy amyloid deposition in the myocardium. Hematoxylin and eosin.  $\times 120$ .  
B. "Amyloid rings" at the periphery of fat cells. PAS stain.  $\times 265$ .

scattered throughout. The most striking finding was the presence of innumerable small papules or nodules (figure 2), measuring a few millimeters in diameter, not unlike the enlarged Peyer's patches found in the terminal ileum and cecum in conditions producing lymphoid hyperplasia. These nodules were most numerous, how-

ever, in the jejunum, although present to some extent throughout the entire small and large bowel, including the rectum. There were no ulcerations. There was no undue rigidity of either stomach or bowel.

*Microscopic Examination:* There was a heavy amyloid deposition in the heart, blood vessels, abdominal fat, abdominal lymph nodes, spleen, kidneys, and the entire

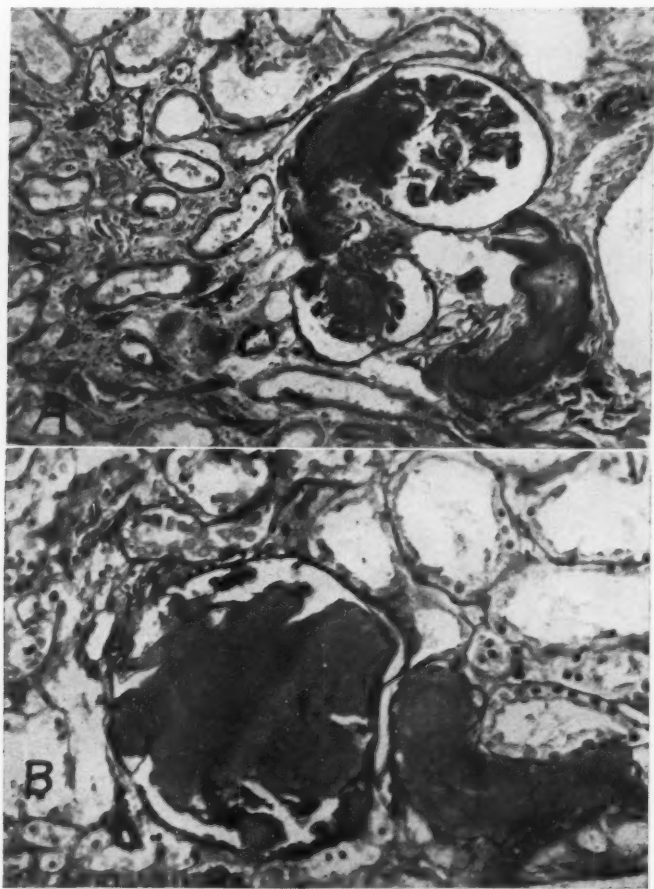


FIG. 4. A. Amyloid deposition in kidney, with partial obliteration of arterioles and glomeruli. PAS stain.  $\times 120$ . B. Massive obliteration of arteriole and glomerulus. PAS stain.  $\times 265$ .

gastrointestinal tract, including the esophagus and rectum, and lesser amounts in the liver (in relationship to hepatic artery radicles) and adrenals (figures 3, 4 and 5).

The spleen and liver contained small focal collections of foamy histiocytes negative for acid-fast organisms, representing involuted miliary lepromas.

The kidneys contained massive amyloid deposits, primarily in relation to small and medium sized arterioles, with partial or complete obliteration of many glomeruli

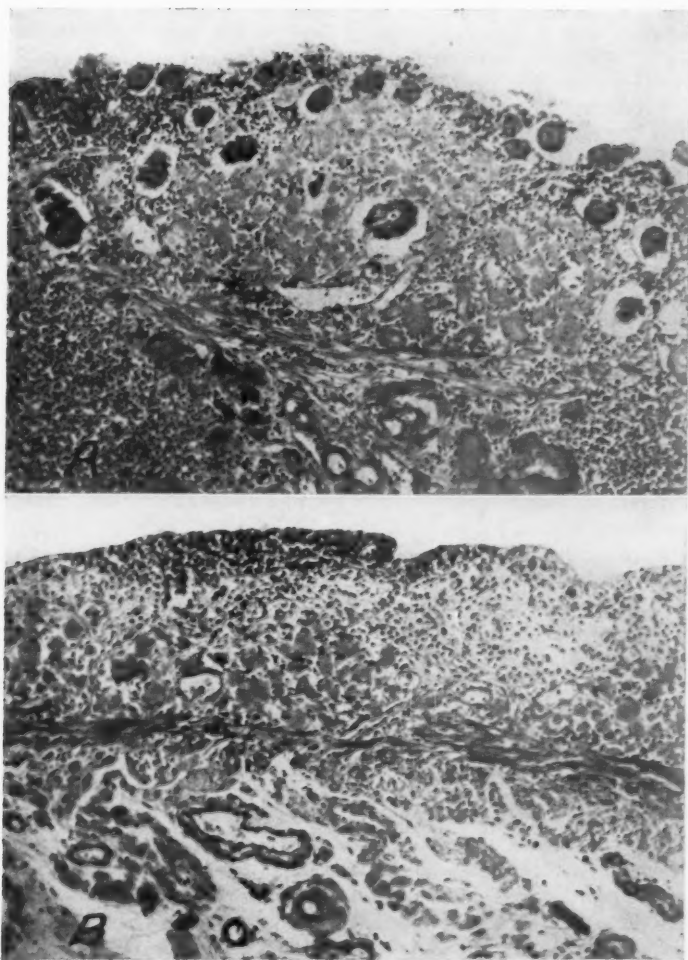


FIG. 5. A. Amyloid deposition in jejunum, with destruction of glands producing the minute mucosal nodules noted grossly. Heavy involvement of submucosal vessels is apparent beneath the frayed muscularis mucosae. PAS stain.  $\times 120$ . B. Complete destruction of glands of jejunum, with thinning of the lamina propria and focal deposits of amyloid just above the thin muscularis mucosae. PAS stain.  $\times 120$ .

(figure 4). Some were completely obliterated, as shown in the illustration, while in others much smaller deposits were present, but there was hardly a glomerulus which did not show some amyloid deposition. Toward the pelvis, massive deposits were present between collecting tubules. Many focal hemorrhages were present, but there was little or no scarring.

Many blocks of tissue were examined from various parts of the gastrointestinal tract, and the pattern of involvement is shown in figure 5. The amyloid was con-

lined chiefly to the lamina propria of the mucosa and to arterioles in the submucosa. In some fields, solid conglomerate deposits were present, with destruction of glands (figure 5 A), thought to represent the small mucosal nodules noted grossly. In other fields the epithelium was entirely missing, the lamina propria much thinner than normal, and there was a more or less continuous band of "globlike" amyloid deposits just above the muscularis mucosae (figure 5 B). The loss of the epithelium was not due to postmortem desquamation, because in many fields a lining of very thin but intact epithelium could be seen. No amyloid could be demonstrated in the muscle coat of the bowel, which is at variance with some of the reported cases.

The amyloid stained a brilliant orange-red with Congo red, and a much darker purple-red with the periodic acid-Schiff stain. The latter technic gave uniformly reliable and consistent results, and we prefer this method over all others for the demonstration of amyloid.

#### DISCUSSION

The clinical and laboratory findings were diagnostic of the malabsorption syndrome, but the radiographic appearance of the bowel was at variance with cases of sprue (idiopathic steatorrhea), in which intestinal dilatation can usually be demonstrated. Anemia is often present in sprue, whereas in our case the erythrocyte and hemoglobin values were normal. The presence of albuminuria and moderate microhematuria, associated with a normal blood urea nitrogen and  $\text{CO}_2$  combining power, led to a consideration of amyloidosis in the differential diagnosis, particularly in view of the high incidence of this condition in patients with lepromatous leprosy. Subsequent biopsy of the jejunum and the later necropsy studies did show extensive amyloid deposition in the kidneys, heart and gastrointestinal tract, and provided a perfect organic background for the clinical picture.

A number of conditions in addition to amyloidosis may produce organic involvement of the intestine, with impairment of the absorption mechanism, and malignant neoplastic disease is perhaps the most common of these. The bowel may be so severely involved that it is unable properly to absorb any nutrients, including carbohydrates, proteins, vitamins, minerals and electrolytes, in addition to fats. A technic has recently been introduced in which triolein and oleic acid are tagged with radioactive iodine, providing a simple and reliable method for the detection of malabsorption states, and this procedure holds much diagnostic promise for the future. Hypokalemia with muscle weakness, mental apathy, loss of reflexes and electrocardiographic changes is often responsible for death in patients with idiopathic steatorrhea, and this may have been the immediate cause of death in the patient herein reported.

#### SUMMARY IN INTERLINGUA

Un revista del litteratura ha monstrate que amyloidosis enteric, ben que relative-mente commun, resulta raramente in un syndrome de malabsorption. Le facto que amyloidosis es un complication frequente de lepra lepromatose non es generalmente appreciate. Materiales necroptic ab 17 ex 37 patientes con lepra qui moriva a Kalaupapa, Molokai (Hawaii), contineva amyloide; e 15 de iste 17 patientes habeva le forma lepromatose del morbo.

Es reportate un caso de character distinctemente inusual. Un juvene adulto masculine japonese, victima de lepra lepromatose e exhibiente omne le characteristics clinic de syndrome de malabsorption, esseva recognoscite in vita como portator de

amyloidosis intestinal. Le constataciones clinic e laboratorial esseva diagnostic pro-sindrome de malabsorption, sed le apparentia radiographic del intestinos tenue e crasse esseva inusual. Le expositiones supero-gastrointestinal monstrava un marcate disturbance del configuration mucosal in le intestino tenue, con restringimento e un grossier configuration nodular del mucosa in le jejuno. In le colon le normal configuration mucosal se habeva perditte completamente.

Le biopsia del jejuno—e subsequentemente le studios necroptic—revelava pesante depositos de amyloide in le corde, le vasos de sanguine, le grassia abdominal, le nodos lymphatic del abdomine, le splen, le renes, e le complete tubo gastrointestinal, incluse mesmo le esophago e le recto.

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#### FATAL TOXIC REACTION TO AMPHOTERICIN B IN CRYPTOCOCCAL MENINGO-ENCEPHALITIS \*

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*Cryptococcus neoformans* (*Torula histolytica*) causes a subacute or chronic meningo-encephalitis which is uniformly fatal. The duration of illness may vary from about three weeks <sup>1</sup> to almost 16 years <sup>2</sup> after the onset of symptoms.

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The majority of patients succumb within six months of onset, and from 80 to 90% of patients are dead within the first year.<sup>3</sup> The tendency toward remissions and exacerbations in this disorder has made difficult the evaluation of therapy. In the past, treatment of torular meningo-encephalitis has been ineffective. However, in 1957 Appelbaum and Shtokalko<sup>4</sup> reported arrest of the disease for seven months in a patient given amphotericin B (Fungizone). Since then a number of studies<sup>5-10</sup> have tended to confirm this drug-effect in the disease. The following case is presented not only to show the laboratory efficacy of this agent, but also to call attention to the cytotoxic potentials of amphotericin B.

#### CASE REPORT

A 32 year old right-handed Negro laborer was admitted to the Neurology Service on January 7, 1958, with a progressive paraparesis of some 18 months' duration. His illness began in the summer of 1956 with headache, anorexia, urinary urgency, enuresis, and weakness of the legs. There had been insidious progression thereafter until this admission. Over this period the patient had been hospitalized elsewhere four times with, in each instance, spastic paraparesis demonstrated. Repeated spinal fluids showed pleocytosis (60 to 375 white cells, with the majority mononuclear), protein elevated to 360 mg.%, sugar as low as 10 mg.%, and chlorides under 700 mg.%. Cultures for organisms including fungi and acid-fast bacteria had been negative, and no definitive diagnosis was made. Attempted pneumoencephalograms revealed nonfilling of the ventricular system.

Upon admission the patient weighed 70 Kg. Neurologically he showed marked mentation defects, with impaired memory, orientation, calculation, judgment and insight. There was a first degree nystagmus. Gait was spastic-ataxic, all extremities were hyperreflexic, and the lower limbs revealed diffuse wasting, moderate weakness, spasticity, and bilateral Babinski's signs. Spinal fluid findings are summarized in the accompanying chart (figure 1). Spinal fluid cultures were consistently negative, including those on Sabouraud's medium, and it was not until March that an India ink preparation was inspected. This revealed numerous organisms with a large, clear capsule. Several later fluids also showed these organisms. A periodic acid Schiff stain demonstrated a budding fungus. Sealed wet India ink preparations also showed budding of the organisms after one week (figure 2).

Mycostatin, 1,000,000 units four times daily, was administered from March 27 to May 12. Spinal fluids on May 7 and May 21 were essentially the same as the earlier ones: over 300 white cells (three quarters lymphocytes), protein over 250 mg., sugar about 20 mg., chlorides 690 mg., and a paretic colloidal gold curve. Serologic tests for syphilis were always negative.

Amphotericin B was initiated on May 20, with 20 mg. diluted in 500 c.c. of 5% glucose given intravenously over a period of six hours. The dosage was gradually raised to 60 mg. a day. At first the patient experienced no systemic ill effects. From the second week he had nausea with vomiting, chills, and low grade fever. Hematuria, anemia, and a rise in blood urea nitrogen from 12.5 and 14.5 mg.% to 18 and 25 mg.% necessitated discontinuation of the drug on June 19. On June 26 blood urea nitrogen was 36, and on June 30, 44 mg.%. By July 8, it was 25 mg.%, and on July 17 had fallen to 17 mg.%. From normal levels, hemoglobin dropped to 9.5 gm.% with a hematocrit reading of 26. Bleeding and clotting times were normal. The patient had received a total of 1.21 gm. of amphotericin. Hematuria ceased by early July, and the blood count returned to 11.7 gm.% hemoglobin with a hematocrit of 31 by July 18, later reaching normal levels without specific therapy. The next lumbar puncture after May 21, done on June 10, revealed 85 white blood cells (59%



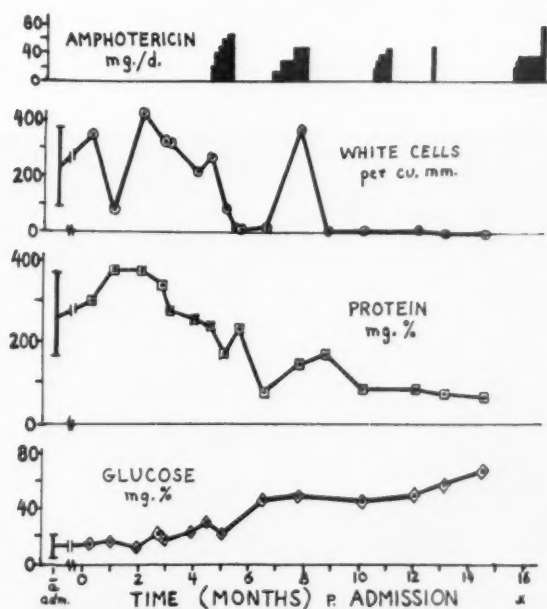


FIG. 1. Summary of spinal fluid findings correlated with courses of amphotericin B, with dosage noted as total milligrams per day.

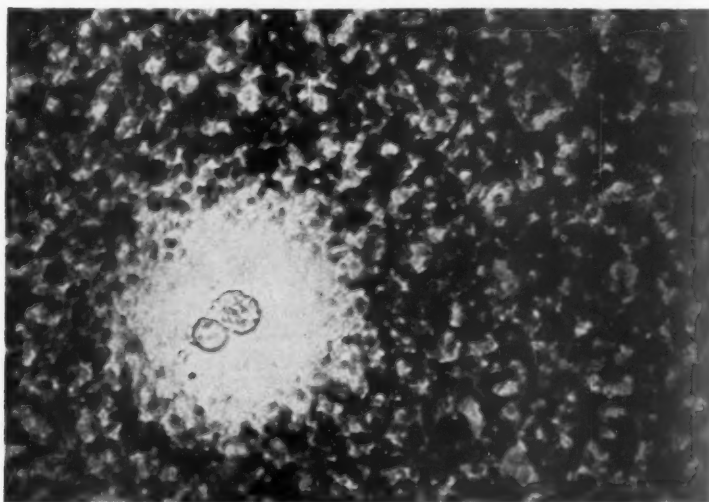


FIG. 2. India ink preparation of spinal fluid sediment of July 24; picture taken five days after sealed wet mount made; note budding of the organism, which is the size of a lymphocyte.

lymphocytes); protein, 175; sugar, 21; chlorides, 690 mg.%. On June 24, spinal fluid cell count was 7 and protein, 238 mg.%. On July 24, cell count was 22, all mononuclear, but on India ink smear they seemed to be all cryptococci. Protein then was 75, sugar, 46, and chlorides, 720 mg.%.

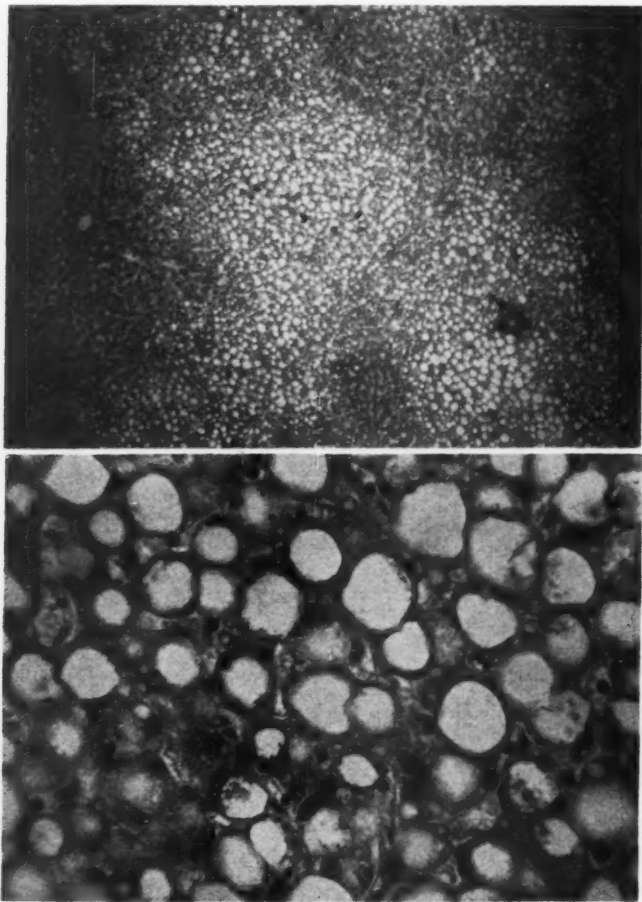


FIG. 3A (*above*) and B (*below*). Liver sections, hematoxylin and eosin stain; note marked centrilobular fatty infiltration and degeneration, lack of inflammatory cells, and pigment (amphotericin?) in Kupffer's cells. (A: 50 $\times$ ; B: 430 $\times$ ).

On this date, amphotericin B was re-instituted, at 16 mg. per liter of 5% glucose. The patient developed nausea and low grade fever. Benadryl, 25 mg., or Pyribenzamine, 50 mg., was added to the infusion, and these side-effects disappeared. Dosage of Fungizone was slowly increased to 50 mg. daily. The blood urea nitrogen and blood count remained within normal range throughout this course, which totaled 1.22 gm. By early September, treatment had to be discontinued because of thrombo-

phlebitis and shortage of accessible veins. Where the solution extravasated a cellulitis was produced, with edema of the limb. By the end of December the patient had deteriorated considerably. He was essentially bed-ridden, and his dementia had worsened.

Between mid-November, 1958, and the latter part of January, 1959, with the use of venous cutdowns and polyethylene catheterization, it was possible to give only 0.78 gm of the antibiotic because of thrombophlebitis and edema. Adding 20 mg. heparin to the infusion did not lessen this effect. Spinal fluid on August 28 revealed 365 white blood cells (73% lymphocytes); protein, 145; sugar, 49; chlorides, 750 mg.%. On September 25 there were 6 white blood cells; protein, 175; on November 12, 11 white cells were present, with protein, 90; sugar, 46; chlorides, 720 mg.%. No treatment was given thereafter until April 21, 1959. The spinal fluid on February 16 showed no cells; protein, 76; sugar, 58; chlorides, 730 mg.%. On March 17 there were again no cells; protein, 70; sugar, 68; chlorides, 720 mg.%; globulin was

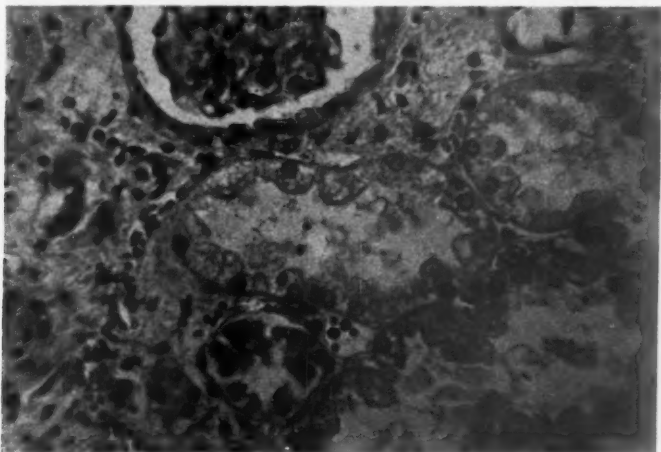


FIG. 4. Kidney section, hematoxylin and eosin stain, 430 $\times$ . Note swollen tubules, with some degeneration of the lining cells.

positive, and the colloidal gold curve was once more paretic. No later taps were performed, because of sacral decubiti. The patient remained bed-ridden and demented.

Due to lack of clinical improvement, it was decided to repeat a course of Fungizone. On April 21, 20 mg. amphotericin, with Benadryl, 25 mg., and heparin, 20 mg., in 500 c.c. of 5% glucose solution, was begun, using cutdowns. Because of the absence of patent superficial veins, a catheter was inserted directly into the femoral vein by an open procedure on April 28, and thereafter 40 mg. a day were given until May 27, when the use of 80 mg. was begun. Medication was discontinued on June 1, and total dosage in this course amounted to 1.61 gm. At the time the patient weighed 80 Kg.

Throughout this period there was no overt clinical or laboratory change until the evening of May 30, when the patient spiked a temperature of 103° F., vomited, and passed dark urine. Liver function tests, blood urea nitrogen and urine of May 27 were normal. On June 1 a large, tender liver was palpated, and all medication

was stopped. The patient had been receiving moderate doses of chlorpromazine for the last five months. He continued to be acutely ill. On June 3 dyspnea, rapid pulse, distended abdomen, and signs of a right lower lobe pneumonia were noted. Urine of June 1 showed a specific gravity of 1.007, more than 200 mg.% albumin, and innumerable red blood cells and white blood cells. It was negative for urobilinogen and sugar. Serum bilirubin on the same day was 1.4 mg. (0.2 direct); alkaline phosphatase 4.0; thymol turbidity, 1.1; cephalin flocculation, 4 plus in 24 hours. The patient died at 10:30 a.m. on June 3, 1959.

*Autopsy Findings:* \* Autopsy performed the same day revealed congestion of the lungs, with petechial hemorrhages and a mild bronchopneumonia. The liver weighed 3,115 gm., and was friable and markedly congested. It was a mottled reddish brown and light yellow, both on the surface and on cut section. The kidneys weighed 750 gm. together, and were pale and pinkish yellow. The corticomedullary border was



FIG. 5. Medulla and meninges, ventral portion; note chronic arachnoiditis, lack of inflammatory cells, demyelination of pyramids. Periodic acid Schiff—luxol fast blue stain, 100  $\times$ .

indistinct, and several petechial hemorrhages were seen in the cortex of the right kidney. Other viscera were essentially normal.

The brain weighed 1,415 gm. in the fresh state. Upon sectioning in the fixed state, the leptomeninges were seen to be thickened, especially over the fourth ventricle, the base of the brain and the ventral brainstem. There was no hydrocephalus, but the aqueduct was mildly dilated. About the spinal cord there was marked thickening of the meninges, with matting around the roots.

Microscopically the liver, kidneys and brain showed the following picture: In the liver (figures 3A and B) there was marked central lobular fatty infiltration, with moderate fatty metamorphosis but no inflammatory reaction. Areas of bile pigmentation suggestive of stasis and some degree of hepatic failure were seen. Kupffer's cells filled with pigment were scattered throughout the degenerated portion of the lobules. The type of degeneration was suggestive of that seen in chemical poisoning rather than in hepatitis. The diagnosis was toxic hepatic degeneration.

\* Our thanks are due to Dr. Frank B. Lynch, Jr., for the general pathologic examination, and to Dr. Richard G. Berry, for the neuropathologic description.

In the kidneys (figure 4) the glomeruli were relatively unaffected. There was mild congestion. The periglomerular capsule was the site of acute inflammation. In the proximal tubules there was mild granular degeneration, with definite diminution of nuclei. Distal tubules were relatively unaffected by the degenerative process, but many of them contained pus. The pathologic diagnosis was toxic degenerative nephrosis with incidental ascending pyelonephritis.

Numerous brain sections showed a marked chronic inflammatory response in the leptomeninges, more marked at the base of the brain (figure 5). Cortically, in the left superior and midfrontal gyri, there were occasional ghostlike neurones, with some proliferation of microglia into rod cells and a minimal perivascular reaction. There was considerable gliosis in the fibrous white matter in Ammon's horn, with a rare "granulomatous reaction." In the pons there were focal scars of glial reaction, with areas of acute softening. The basilar artery was markedly sclerotic. The

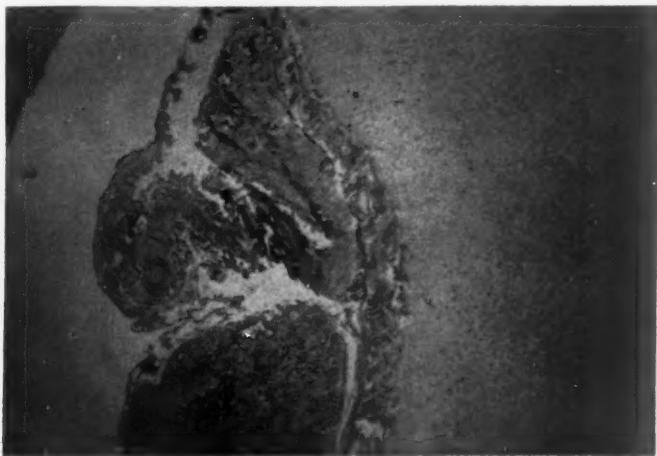


FIG. 6. Midthoracic spinal cord, ventrolateral portion. Note compression of cord by the arachnoiditis, with superficial demyelination, most marked in corticospinal and spinocerebellar tracts; note lack of cellularity in the area of arachnoiditis. A ventral root is seen at bottom of picture. Periodic acid Schiff—luxol fast blue stain, 100 $\times$ .

pyramids were poorly stained. In the spinal cord there was loss of myelin in some of the roots, particularly in the cauda equina. There was thickening of the pia-arachnoid. The midthoracic cord showed shrinkage of the spinocerebellar and corticospinal tracts, with demyelination (figure 6). There was no evidence by periodic acid Schiff or metachromatic stains of residual cryptococci. The diagnoses were chronic leptomeningitis and encephalitis; presumed etiology, *Cryptococcus neoformans*.

#### DISCUSSION

A 32 year old Negro male with cryptococcal meningo-encephalitis was treated with amphotericin B. Over a period of one year he received a total of 4.82 gm. of this agent in four separate courses. During this time, although his spinal fluid reverted toward normal, he showed no clinical improvement, but rather deteriorated.

The drug, dissolved in 5% glucose solution to a concentration of 0.1 mg. per cubic centimeter and given intravenously, purportedly has only minor complications.<sup>6</sup> In our case, much less concentrated solutions caused severe thrombophlebitis in spite of concurrent use of heparin. This was the major limiting factor in its administration.

Nausea and vomiting induced by this agent were adequately controlled by antihistamines. The mechanism underlying this side reaction of seemingly minor importance is unknown, as is that for the efficacy of antihistamines.

An elevation of blood urea nitrogen after administration of 1.2 gm. amphotericin B disappeared upon cessation of medication. This has been observed by others.<sup>6-10</sup> Utz and Treger<sup>8</sup> found such a rise in 30 cases, and had to reduce the dose or interrupt treatment for a few days. However, "in all instances the toxic effects were reversible at the end of therapy."<sup>8</sup> Even though the patient's blood urea nitrogen remained normal in later courses of the drug, there were definite pathologic changes in the kidney, some of which appeared to be toxic in origin and were of short duration. The hematuria seen was probably due to a combination of his pyelonephritis and drug toxicity.

Out of 90 patients reported as treated with amphotericin B for systemic mycoses,<sup>6-10</sup> only one possibly experienced liver toxicity due to medication.<sup>6</sup> The cause was questionable to the reporters even after liver biopsy. In our case, the picture was one of an acute toxic degeneration of the liver, and the symptoms coincided with the increased dosage (80 mg. = 1 mg./Kg./d.), which was given for but three days. The immediate cause of death was considered to be this acute hepatic failure. The pathologic picture, moreover, was quite dissimilar to that seen in chlorpromazine jaundice, and no other medication was received by the patient.

As to the basic disease, an intensive search revealed no cryptococci, and earlier the spinal fluid had been practically normal. Another instance is therefore present suggesting the therapeutic efficacy of amphotericin in torular meningo-encephalitis. The lack of clinical improvement was explicable by the degree of adhesive arachnoiditis and secondary vascular changes. The necessity of early diagnosis and treatment is emphasized.

#### SUMMARY

1. A case is presented of chronic torular meningo-encephalitis treated with amphotericin B. The efficacy of amphotericin B in clearing the tissues of cryptococci was demonstrated, but clinical improvement was not seen because of the adhesive arachnoiditis.

2. Reported toxic effects of amphotericin B were confirmed. Fever, nausea and vomiting occurred and were controlled by antihistamines. Elevated blood urea nitrogen disappeared on cessation of the first course of the drug and did not recur when it was repeated. Heparin and dilution of the drug beyond that recommended failed to prevent chemical phlebitis. A catheter inserted directly into the femoral vein was necessary to make possible the administration of an adequate dose.

3. After three days' administration of amphotericin B at 1 mg./Kg./d., which followed one month at the daily dose of 0.5/mg./Kg./d., the patient became



acutely ill and died two days later. Autopsy demonstrated acute toxic degeneration of the liver and toxic nephrosis.

#### SUMMARY IN INTERLINGUA

Un negro de 32 annos de etate eseva hospitalisate con paraparesi progressive de 18 menses de duration. In le curso de iste intervallo ille habeva sojornate a un altere hospital ubi repetite examines de liquido spinal habeva monstrate pleocytosis, augmentos de proteina, basse valores pro sucro e le chloruros, e negativitate de culturacion. Post su admission al hospital del Administration de Veteranos a Coatesville, Pennsylvania, le patiente manifestava dementia partial, nystagmo, e debilitate spastico-ataxic in le extremitates inferior. Examines de liquido spinal produceva repetitemente le mesme resultatos, a generalmente parlar: Circa 300 leucocytos con predominantia lymphocytic, proteina de plus que 250, sucro de circa 20, e chloruros de 690. Organismos de torula eseva demonstrate in le liquido spinal per medio de preparatos a tinta de China. Amphotericina B eseva administrate durante un mense, initialmente in un dosage de 0,3 mg per kg de peso corporee per die, augmentate usque al maximo de 0,8 mg per kg per die. Nausea, vomito, algor, e basse grados de febre eseva subjugate per medio de antihistaminas. Le curso de amphotericina B eseva interrompite a causa de hematuria, anemia, e uremia. Le curso eseva repetite tres vices durante le sequente septe menses. In omne le casos illo eseva terminate a causa de phlebitis chimic. Le liquido spinal eseva essentialmente normal a partir del none mense post le hospitalisation, sed le stato clinic del patiente continuava deteriorar se. Dece-cinque menses post le admission al hospital, le patiente recipeva le ultime curso de amphotericina B. Le curso durava un mense. Le dosage eseva 0,5 mg per kg per die, e le administration eseva effectuate via un catheter implantate in le vena femoral. Postea le patiente recipeva 1,0 mg per kg per die, sed ille deveniva acutemente malade, con febre, vomito, urina obscur, e hepate allargate e hyperesthetic. Le medication eseva interrompite, e le patiente moriva duo dies plus tarde. Le constataiones pathologic includeva un peso hepatic de 3.115 g e le presentia in le hepate de un marcate infiltration grasse de loco centrolobular. Le renes eseva tumefacite, e le constataiones histologic reflecteva nephrosis toxic. Un chronic leptomeningitis adhesive eseva presente, specialmente circum le base del cerebro e le medulla spinal. Nulle organismos poteva esser trovate. Eseva concludite que le causa de morte eseva acute degeneration toxic del hepate.

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### CARCINOMA OF THE HEAD OF THE PANCREAS, A LONG-TERM SURVIVAL \*

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IMPETUS for the application of the principles of radical cancer surgery to carcinoma of the pancreas and ampullary region was given by Whipple and associates beginning in 1935.<sup>18-20</sup> Since the introduction of pancreatoduodenectomy for cancer of the head of the pancreas, the reported cases of patients surviving five years or longer after operation have been very few.<sup>3, 4, 8, 11-14, 17</sup>

The following case is reported as a long-time survival following surgery for carcinoma of the head of the pancreas.

#### CASE REPORT

A 49 year old Negro male was first admitted to the medical service of the Philadelphia General Hospital on August 8, 1949. He admitted to a heavy consumption of alcohol for from 20 to 30 years, and for the two years prior to admission had consumed at least a quart of wine per day. The patient had been asymptomatic until six weeks before, when he began to notice weakness and fatigue. An annoying, nondescript epigastric pain, not particularly bothersome, had been present for a month. During the 10 days before admission he had been troubled by itching, especially at night, and had noticed a yellow color of the sclerae.

Physical examination revealed weight loss, jaundice, and an enlarged, smooth, nontender liver.

After extensive studies it was felt that the patient was suffering from an obstructive type of jaundice, and surgery was recommended. On September 2, 1949, surgery was performed. A distended gall-bladder and common bile duct were seen. The distended common duct extended into the head of the pancreas, which was hard, indurated and nonfixed. A tumor mass was felt in the head of the pancreas.

A pancreatoduodenectomy was done. Three anastomoses were performed, starting proximally and going distally: the fundus of the gall-bladder was anastomosed to the jejunum, an anastomosis of the remaining portion of the pancreas and pancreatic duct to the jejunum was done, and then a gastrojejunostomy was completed.

Inspection of the gross surgical specimen revealed an almost annular compression of the common bile duct 2 cm. from the ampulla of Vater by a tumor about

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1 to 2 cm. in size that appeared to arise in the adjacent pancreatic tissue. Microscopic examination showed an adenocarcinoma of the head of the pancreas (figure 1).

The only postoperative complication was gastrointestinal hemorrhage on September 10, with falling blood pressure and hemoglobin. These responded to trans-

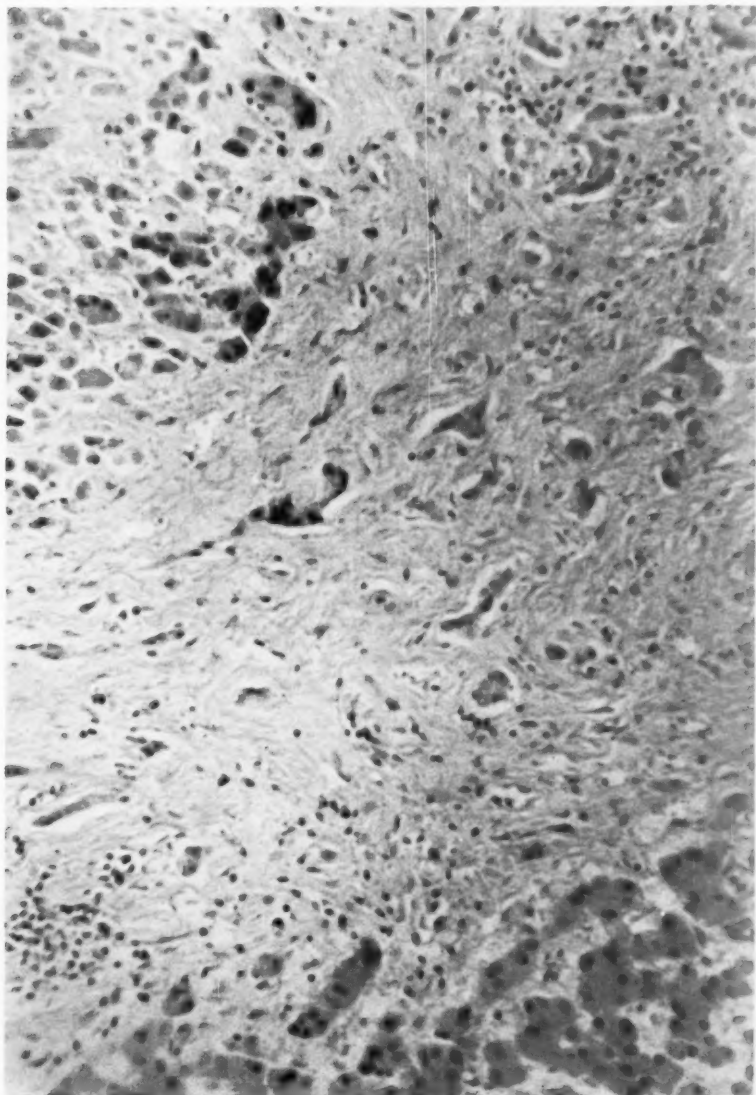


FIG. 1 A and B. Photomicrographs of section of pancreas removed in September, 1949, demonstrating carcinomatous tissue composed of irregular ductlike structures and sheets of anaplastic cells. A, hematoxylin and eosin stain,  $\times 45$ .

fusions, and the bleeding stopped. The patient was discharged on September 22, to be followed in clinic.

Between October, 1949, and May, 1958, the patient was admitted to the hospital a total of 15 times. The complaints on these admissions were: shaking chills, fever, right upper quadrant pain, and at times, nausea and vomiting. The opinion of the

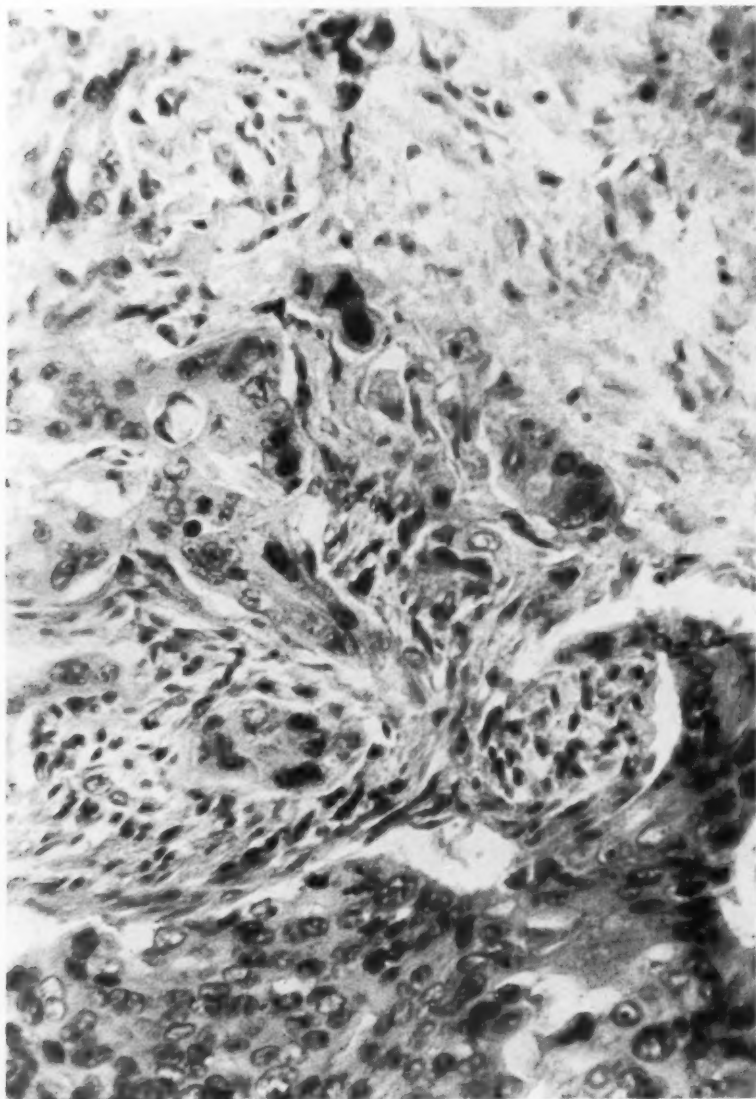


FIG. 1 B. Hematoxylin and eosin stain,  $\times 295$ .

medical staff was that the signs and symptoms were due to ascending cholangitis. These attacks subsided on treatment with antibiotics and supportive therapy.

In May, 1950, after a period of observation showed increasing jaundice, a laparotomy was done. A diagnosis of stenosis of the cholecystojejunostomy stoma was entertained preoperatively. At operation, the junction of the original cholecystojejunostomy would admit only a very small probe. A revision of the anastomosis was done. The liver showed characteristics of biliary cirrhosis. There was no evidence of metastasis or of the original disease.

During these many admissions there was gradual development clinically of increasing size of a hard, nodular liver, ascites, and clubbing of the fingers and toes. Laboratory examinations over the years showed progressive hepatic dysfunctions. Table 1 is a random selection of a few of the hepatic function tests done on this patient, illustrating progression of hepatic malfunction.

On June 1, 1958, after passage of several tarry stools, hyperactivity with delirium and flapping tremor developed. The patient was treated for bleeding esophageal varices and impending hepatic coma. He gradually recovered and was discharged. X-rays after this episode revealed esophageal varices for the first time.

The seventeenth and final postoperative admission occurred for this patient on July 29, 1958. He was brought in in coma, with a blood pressure of 72/40 mm. Hg. In spite of vigorous treatment he died within three hours.

TABLE 1  
Progression of Hepatic Dysfunctions in a Case of Biliary Cirrhosis

Date	Cephalin Flocculation	Thymol Flocculation	Thymol Turbidity	Cholesterol	Esters %	A/G Ratio
August, 1949	0	0	0	295	69	5.0/2.7
June, 1953	0	0	1.6	318	62	4.7/4.4
March, 1957	3+	4+	5.8	174	46	4.1/5.3
May, 1958	3+	1+	8.2	265	23	4.0/4.3

At postmortem examination the abdominal cavity showed the stomach and the descending and transverse colon to be adherent to the inferior surface of the liver. There were esophageal varices, with evidence of rupture at one point, and 200 c.c. of blood in the stomach. The liver weighed 2,600 gm., had a nodular surface, and was green in color. Multiple abscess cavities of various sizes containing greenish yellow purulent material showed on the surface and on sectioning of the liver. Gross sectioning also revealed dilated intrahepatic biliary ducts. The pancreatic duct was patent. The spleen weighed 600 gm. and on sectioning showed congestion.

Microscopic tissue examinations revealed biliary cirrhosis and abscesses with bacterial colonies. Acute necrosis of some liver lobules was seen. The remaining pancreas showed a mild increase in interstitial fibrosis. No microscopic signs of carcinoma were found in any organ.

#### COMMENT

The opinion that painless jaundice is the most common symptom of carcinoma of the pancreas is still widely held and taught. Many authors have attacked this long-standing opinion.<sup>1,2,4-7,9,10,15</sup> Stenstrom and Ford, in their article summarizing the symptoms in 159 proved cases of carcinoma of the head of the pancreas, found upper abdominal pain first, as to both initial symptom and

frequency.<sup>17</sup> This patient's annoying epigastric pain began approximately three weeks before the onset of jaundice.

This patient had been an alcoholic for from 20 to 30 years before his first hospital admission. After pancreatoduodenectomy for carcinoma of the head of the pancreas he suffered many attacks of cholangitis. Chronic infection, cirrhosis, esophageal varices with hemorrhage, shock, hepatic necrosis and liver failure eventually resulted in death. The evolution of Whipple's original operation— anastomosis of the gall-bladder to the stomach—has shown that implantation of the common bile duct into the jejunum is the best of several procedures. Anastomosis using the gall-bladder increases the chances of reflux infections and occlusion of the anastomotic site.<sup>8</sup> This patient developed stenosis of the cholecystojejunostomy stoma and underwent a second operation for this correction. An anastomosis of the common duct to the jejunum, if it had been possible during the original operation, might have prevented some of the attacks of cholangitis and prolonged his life. At no time did he show signs of diabetes or other pancreatic dysfunction, clinically or by laboratory examination.

The smallness of the carcinoma and its location adjacent to the common bile duct, together with the absence of metastasis at the time of surgery, contributed to a favorable prognosis with respect to the neoplasm. This could not have been adequately determined except by abdominal exploration, resection and examination of the specimen. With these favorable findings in a patient, an attempt at complete resection and maximal effort at supportive therapy seem to be justified.

#### SUMMARY

A case of carcinoma of the head of the pancreas in a patient who survived for eight years and 11 months after radical surgery is presented. Operation was followed by numerous attacks of cholangitis that terminated in biliary cirrhosis with esophageal varices. At portmortem examination no evidence of carcinoma was found.

#### SUMMARIO IN INTERLINGUA

Pancreatoduodenectomia como tractamento definitive pro carcinoma del capite pancreatic e del region ampullari es usate plus frequentemente deposite le publicationes de Whipple e su associatos relative a iste methodologia. Tamen, mesmo con le abandono de mesuras de typo palliative in favor del principios de chirurgia radical que visa al ablation del totalitate del tissu maligne, reportos de quinquenne superviventia post chirurgia pro carcinoma del capite pancreatic non ha devenite numerose.

Le masculo de qui le presente reporto relata le historia clinic habeva 49 annos de etate quando ille se hospitalisava in agosto 1949 a causa de vage dolores epigastric de un mense de duration con ictero de un duration de 10 dies. Le investigation del caso resultava in le impression de un jalnesa obstructive. Le intervention chirurgic revelava un distendite vesica biliari. Etiam le commun ducto biliari esseva distendite, e un tumor esseva presente in le capite del pancreas. Pancreatoduodenectomia esseva effectuate in concomitantia con cholecystojejunostomia, gastrojejunostomia, e pancreatojejunostomia utilisante le remanente partes del pancreas e del ducto pancreatic. Le examine pathologic del specimen de excision chirurgic revelava adenocarcinoma del capite pancreatic.

Le patiente esseva re-hospitalisate 17 vices inter octobre 1949 e le tempore de su morte in julio 1957. In le majoritate del casos, le motivo del hospitalisation esseva



algor con febre, dolores in le quadrante dextero-superior, e nausea e vomito. In maio 1950, le stoma cholecystojejunostomic eseva revidite a causa de stenosis resultante in augmento de jalnessa. Le curso clinic in le sequente annos eseva marcate per hepatomegalia progressive con nodularitate e subsequentemente ascite e digitos hippocratic del manos e pedes. In junio 1957, le hospitalisation del patiente eseva requirite per hyperactivitate, delirio, e un fremito clappante. Le 28 de julio 1957, le patiente eseva hospitalisate in coma, con un tension de sanguine de 72/40 mm de Hg. Ille moriva al fin del prime tres horas al hospital.

Le necropsia monstrava adhesiones abdominal, varices esophagee (con signos de ruptura in un puncto), e un verde hepate nodular que contineva numerose cavitates de abscesso. Le examine microscopic demonstrava cirrhosis biliari, cholangitis, abscessos hepatic, e acute necrosis de certe lobulos del hepate. Nulle signos microscopic de carcinoma eseva trovate in ulla organo.

In le evolution del operation original de Whipple il ha devenite probabile que choledochojejunostomia es melior que anastomose con le uso del vesica biliari in tanto que le possibilitate de infectiones de refluxo e de oclusion stenotic del sito anastomotic es reduceite.

In le presente caso le patiente superviveva le intervention chirurgic per quasi novem annos, e le causa de morte eseva cirrhosis biliari, abscessos hepatic, e varices esophagee in consequentia de numerose ataques de cholangitis, e nulle signo de carcinoma eseva trovate.

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### HETEROTOPIA OF BONE MARROW SIMULATING MEDIASTINAL TUMOR: A MANIFESTATION OF CHRONIC HEMOLYTIC ANEMIA IN ADULTS \*

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A REVIEW of several large series of patients with mediastinal tumors<sup>1, 2, 3, 4, 5, 6</sup> has failed to reveal a single instance of heterotopic bone marrow. As these tumors can grow to a size easily visible on the x-ray film, and as no previous descriptions have been found in the American literature, we report a case recently studied.

Intrathoracic tumors of bone marrow are found only in adults with hemolytic disease of long duration. They tend to increase in size as the hemolytic process continues with advancing age. Most of the well documented cases have been associated with acholuric jaundice or hereditary spherocytosis. A feature which is helpful in distinguishing them from other mediastinal tumors is their characteristic paraspinal location in the inferior mediastinum.

#### CASE REPORT

A 50 year old mine hoist engineer came to the Duluth Clinic on October 28, 1952, because of a pain in the right inguinal region, at the site of a herniorrhaphy performed elsewhere in March, 1952. Upon routine questioning he denied any symptoms referable to the cardiorespiratory system, but did admit that an abnormality had been found on a routine chest x-ray taken two months previously.

The family history disclosed that his father had died at age 70 of heart disease, his mother at age 67 of cerebral hemorrhage. Two brothers, 52 and 54 years of age, were living and well. Another brother had died at birth. There was no familial history of jaundice or anemia.

The past history indicated that he had suffered a severe attack of acute polyarthritis at the age of 25. At this time he had also acquired a penile lesion, for which he received local medication. Thirteen years later (in 1940), a Kahn test was found to be strongly positive, and in 1941 he was given a series of injections in the arms and hip over a six-month period. Many of these were followed by generalized reactions. In 1945 and again in 1952 the Kahn test was reported as negative.

In 1941 a cholecystectomy and herniorrhaphy were performed. In 1945, when a right inguinal herniorrhaphy was performed, jaundice of mild degree was reported.

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However, when this hernia was again repaired in 1951 and in March, 1952, neither jaundice nor splenomegaly was recorded as having been observed. The patient stated that his urine was usually dark in color.

Physical examination revealed a robust, alert man. The following significant findings were noted: The pupils reacted normally to light. Slight scleral icterus was easily seen. Auscultation of the chest was negative. The blood pressure was 126/50 mm. of Hg. At the aortic area and along the left border of the sternum a soft, blowing diastolic murmur was heard. A water-hammer pulse was present. The spleen was enlarged to the level of the umbilicus; it was soft and easily movable. The liver edge could not be palpated. The extremities and tendon reflexes were

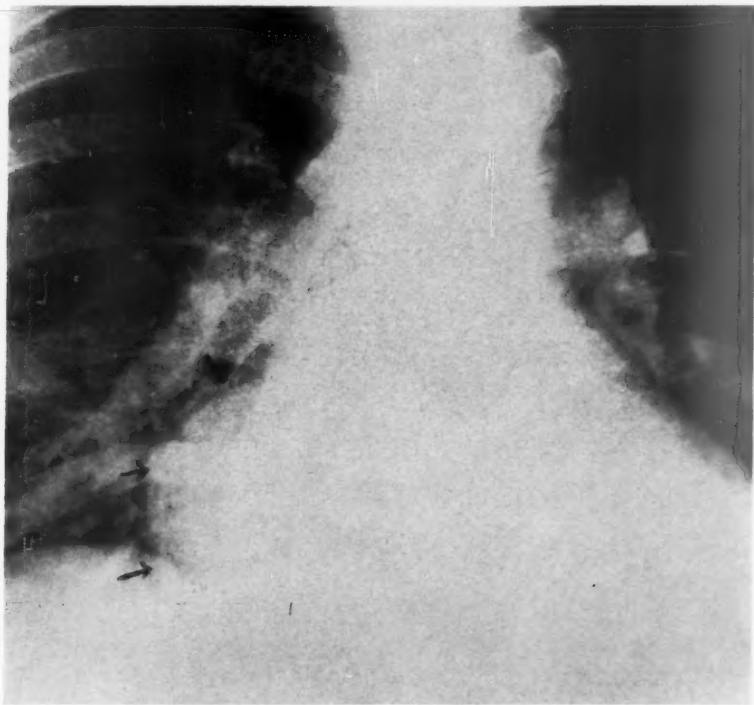


FIG. 1. Frontal chest film (October 1952), showing rounded mass of heterotopic bone marrow.

normal. The site of the right inguinal herniorrhaphy, done in March, 1952, was well healed but tender. No enlarged lymph nodes were palpated; no petechiae were seen.

The following pertinent laboratory findings were obtained from previous hospital records: In 1941 the erythrocyte count was 3.8 million; hemoglobin, 89%; leukocytes, 9,200; and anisocytosis, polychromatophilia and spherocytes were present. In March, 1952, the erythrocyte count was 4.1 million, leukocytes, 7,500, and nucleated red blood cells were seen.

Hematologic data obtained on the initial Duluth Clinic examination were as follows: erythrocytes, 3.7 million; hemoglobin, 10.3 gm.; leukocytes, 12,600; platelets,

176,000; and reticulocytes, 3%. The differential blood count was neutrophils, 76%; bands, 5%; lymphocytes, 15%; and monocytes, 4%. Anisocytosis and polychromatophilia were present; numerous spherocytes were seen. The sedimentation rate was 28 mm. per hour (Cutler). The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was positive (undiluted); Kolmer's test was negative. The blood urea nitrogen was 6.5 mg.%. The serum albumin was 4.2 gm.; globulin, 2.3 gm.%. Liver function tests revealed a

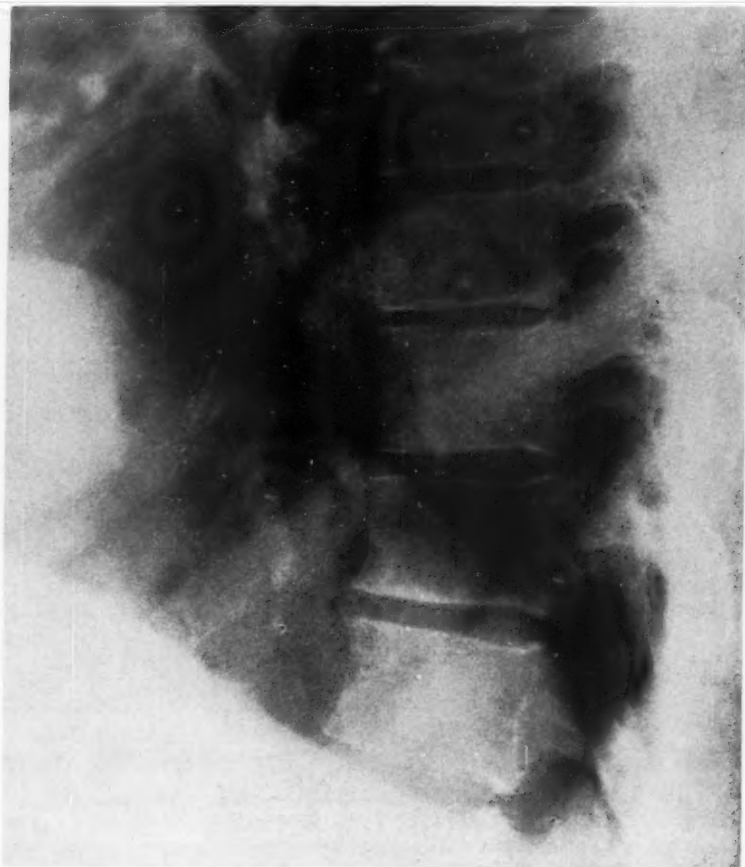


FIG. 2. Lateral film, showing rounded mass overlying T-9, T-10 and T-11.

bromsulfalein retention of 2.5% in 40 minutes; zinc turbidity, 13.5 units; thymol turbidity, 6.5 units; cephalin flocculation, negative; alkaline phosphatase, 6.2 King-Armstrong units. The icterus index was 12. The urinalysis was negative except for 50 to 100 leukocytes per high power field. Bone marrow aspirate showed erythroid hyperplasia, with normal maturation of erythroid and myeloid elements.

X-ray examination of the chest revealed moderate cardiac enlargement and

normal lung fields. Extending laterally from the right cardiac border was a circumscribed mass measuring 8 cm. in diameter which, on a lateral film, was seen to lie in a paraspinal location at the level of T-10 (figures 1 and 2). An overexposed film of the chest revealed not only a distinct round mass on the right but also a smaller rounded mass on the left (figure 3). These masses did not pulsate and were not connected to the esophagus or stomach. A chest film made in 1944 showed the right mass to be faintly visible behind the heart shadow. Another film, taken in 1948,



FIG. 3. Overexposed frontal film, showing large rounded mass on right and smaller mass on left.

showed the same mass to have grown so that it extended slightly beyond the right heart border. A colon x-ray, taken at the present examination, was intrinsically negative, but the splenic flexure was displaced downward and medially by a huge spleen.

Because of the pyuria, the urinary tract was studied further by means of an intravenous urogram and a urine culture. The former showed no abnormality. The urine culture grew out alpha hemolytic streptococci, *Aerobacter aerogenes*, and

*Escherichia coli*. Treatment was started with Terramycin and Mandelamine, and the patient was discharged to his home. No conclusion was reached regarding a diagnosis of the paravertebral tumor and mild hemolytic anemia. Upon the patient's return one month later for further evaluation the urine was normal. The sedimentation rate was 17 mm. per hour, and the hematologic values remained essentially the same as those noted initially.

The diagnoses considered at this time (November 25, 1952) were rheumatic or syphilitic aortic insufficiency with subacute bacterial endocarditis, aneurysm of the aorta, carcinoma of the lung, neurogenic tumor, and lymphoma with secondary hemolytic anemia. Evidence for the diagnosis of aortic insufficiency was unequivocal. The splenomegaly and hemolytic anemia were consistent with subacute bacterial endocarditis, but lack of fever and embolic phenomena, together with the healthy appearance of the patient, were against this diagnosis. The history of syphilis and the location of the tumor suggested aneurysm, but no murmurs were heard over the tumor, and pulsations were absent. It was finally concluded that the heart disease and the mediastinal tumor were unrelated and that each must be considered separately. Cancer of the lung was considered, but the tumor seemed to be clearly extrapulmonary; neurogenic tumor was excluded, as it commonly occurs in a unilateral position. The growth of the tumor was much slower than is usually seen in cancer. The slow growth was consistent with lymphoma, and this diagnosis with secondary hemolytic anemia seemed most likely. It was decided that an exploratory thoracotomy, either for biopsy or for resection, must be done to establish a correct diagnosis.

The patient was hospitalized and a right-sided thoracotomy was performed (R. H. L.) on December 4, 1952. The right pleural cavity was entered, and a firm, dark tumor was seen arising from the posterior chest wall at the level of the eighth rib paravertebrally. A line of cleavage was developed, and by sharp dissection the tumor was removed. It had one-point attachment to the body of the eighth thoracic vertebra by a small, fibrous stalk which contained a vigorously bleeding vessel. The mass was covered by pleura laterally, but mesially was uncovered and lay upon the vertebral structures. The vertebrae were not eroded. The chest was closed, leaving one catheter in place for underwater drainage. Postoperatively a series of complications ensued: atelectasis with pneumonia of the right lower lung, severe paralytic ileus, and the rapid development of anemia and azotemia. The latter occurred despite a satisfactory fluid balance and no evidence of blood loss. Reticulocytosis and icterus were absent. This probably represented a toxic depression reaction or "hemolytic crisis." The patient recovered completely from all of these complications and was discharged to his home on December 30, 1952, with a hemoglobin of 10.9 gm.

The tumor consisted of a mass measuring 6.5 cm. in diameter and 3.7 cm. in thickness, and weighing 72 gm. It presented one dome-shaped surface covered with a smooth membrane, and one flat surface. Microscopically, it was composed of diffusely cellular tissue, consisting of all the blood cells and their precursors as usually found in bone marrow, without definite stroma. There were occasional blood vessels and fat vacuoles supported by fibroconnective stroma. There were also numerous megakaryocytes through the entire structure. Definite erythroblastic proliferation was present, and there were some areas in which hemorrhagic infiltration was abundant. Foci of brown pigment were commonly associated with the hemorrhagic deposits. The tissue presented the appearance of bone marrow. The pathologist's diagnosis was ectopic bone marrow with erythroblastic proliferation.

The patient returned to the Clinic for his first postoperative visit on February 18, 1953. He complained of considerable pain over the surgical scar, but healing was satisfactory. Scleral icterus and splenomegaly were present, as before. A chest



x-ray showed the lung fields to be clear and the tumor on the right side to be absent; the mass on the left was unchanged. X-ray films of the skull and pelvis showed no abnormality. Hematologic studies revealed the following: erythrocytes, 4.18 million; hemoglobin, 86%; leukocytes, 7,000; sedimentation rate, 10 mm. per hour; platelets, 60,000; reticulocytes, 23.9%, with a normal differential blood count. The icterus index was 20. Serum bilirubin was 1.35 mg. indirect, 0.45 direct. Erythrocyte fragility to hypotonic saline showed beginning hemolysis at 0.5%, and complete hemolysis at 0.35%. The direct Coombs' test was negative. The blood group was 0 IV Rh negative. A Donath-Landsteiner test was negative. The patient continued to improve, and returned to work on March 1, 1953. He was observed again on December 9, 1953. After returning to work he had continued to be in good health. Physical findings were the same as previously noted. The erythrocytes were 4.1 million; hemoglobin, 86%; leukocytes, 9,000; reticulocytes, 7.5%; and icterus index, 18. No iso-agglutinins were present.

On March 24, 1957, the patient was re-admitted to the hospital for repair of a recurrence of the right inguinal hernia, and also the repair of a newly acquired left inguinal hernia. Extensive hematologic studies were repeated just prior to his discharge from the hospital. They revealed erythrocytes, 3.2 million; hemoglobin, 10.9 gm.; leukocytes, 11,500; platelets, 271,700; reticulocytes, 10%, with a normal differential count. Spherocytes were present. The icterus index was 18, and the serum bilirubin was 1.0 direct, 3.7 indirect, with a total of 4.7 mg. The direct and the indirect Coombs' tests were negative. Erythrocyte fragility to hypotonic saline began at 0.54% and was complete at 0.33%. A urinalysis was negative except for numerous leukocytes, and a culture revealed a sparse growth of nonhemolytic streptococci. The bromsulfalein retention was 8% in 45 minutes; alkaline phosphatase, 5 King-Armstrong units; serum cholesterol, 110 mg.; thymol turbidity, 6.7 units; serum albumin, 4.0 gm.; globulin, 2.6 gm. Watson's modified quantitative stool urobilinogen was 700 Ehrlich units (normal, 30 to 240).

The latest observations on this patient were made on February 24, 1959. The physical findings remained the same as on the initial examination in 1952, although the left hernia, repaired in 1957, showed signs of recurrence. Hematologic data were as follows: erythrocytes, 3.29 million; hemoglobin, 11.9 gm.; leukocytes, 8,900; differential, normal except for 1 nucleated red blood cell, anisocytosis, polychromasia, and many spherocytes. The reticulocytes were 15%. Erythrocyte fragility to hypotonic saline began at 0.44% and was complete at 0.36%. A control was 0.42% and 0.34%. The sedimentation rate was 14 mm. per hour. Urinalysis was normal, and no urobilinogen was present. The serum bilirubin was 1.0 mg.% direct, 2.7 mg.% indirect, with a total of 3.7 mg.%. An acid lysin test (Ham's test) was negative. Auto-antibody tests for agglutinins were positive at 2°, and negative at 20° and 37°. Tests for hemolysins were negative at 2°, 20° and 37°. These tests were done both on the patient's cells and normal cells. Re-injection of the patient's cells after Cr<sup>51</sup> mixing gave a half-life for the patient's red cells of 14 days (normal, 22 to 26 days). Injection of Cr<sup>51</sup>-tagged normal donor cells into the patient revealed a half-life of 25 days. An x-ray of the chest, when compared with the first post-operative film taken six years previously, showed no change.

Although the increase in erythrocyte fragility to hypotonic saline was slight, the persistent spherocytosis (estimated at 50% or more), the positive evidence of defective red cells, and the absence of an environmental hemolytic factor as determined by radiochromium studies, all supported a diagnosis of hereditary spherocytosis, even though a positive family history was not available. Splenectomy was considered, but, because of his tendency to develop hernias and the many operations already performed on him, the patient has been reluctant to accept this treatment. He now considers himself to be in good health, and works regularly at his job.

## DISCUSSION

The clinical recognition of mediastinal tumors composed of bone marrow is a relatively recent accomplishment. In the past, tumor masses of bone marrow in the mediastinum, as well as in the hilus of the kidney, dura mater, adrenal gland, retroperitoneal region, and hollow of the sacrum, have been found by pathologists only at autopsy or, rarely, at operation. Brannan<sup>7</sup> in 1927 made a comprehensive study of extramedullary hematopoiesis in anemias, and stated that heterotopic marrow masses, wherever located, except in the adrenals, almost always showed a hyperplasia of blood-forming cells, and existed as compensatory hematopoietic tissue in anemic individuals with blood destruction. He thus established a functional connection between such tumor masses of bone marrow and hemolytic anemia which would permit calling this combination a syndrome, and alert clinicians to its clinical recognition when it occurred as a mediastinal tumor.

Intrathoracic heterotopia of bone marrow was first described by Guizetti<sup>8</sup> in 1912. Since then, reports of 16 cases<sup>9, 10, 11, 12, 16 \*</sup> have appeared in the literature, only four diagnosed clinically. Ask-Upmark<sup>9</sup> in 1945 reported the first case. The diagnosis was suspected from the appearance of the tumor on the chest x-ray film, and was proved at autopsy four years later. Paraf et al.<sup>10</sup> reported the second case in 1957. In this instance the diagnosis was proved by needle biopsy of the tumor. Recently, Hanford<sup>16</sup> described two cases. In each of these, multiple mediastinal tumors were observed on the chest x-ray film. In one, the diagnosis was proved by thoracotomy and incisional biopsy, and in the other, by thoracotomy with needle biopsy.

Heterotopic bone marrow tumors in the mediastinum do not produce symptoms; therefore, it is likely that they will most often be detected initially in mass chest x-ray surveys or on routine screening films. They may also be discovered when searched for in any adult patient who has chronic hemolytic disease of long duration. These tumors are always found in the inferior mediastinum lying paraspinally. They vary in size from 2 to 6.5 cm. in diameter, and may be located unilaterally or bilaterally. One tumor may be small and barely visible, while its fellow is large and easily seen on the x-ray film, as in our case. In some cases the tumors have been found lying in segmental formation, with as many as four on a side. Because of their location in the lower half of the chest, the heart shadow is usually superimposed, so that overexposed frontal and lateral films may be necessary for clear visualization. A feature of these tumors, shown in our case and also noted by Paraf, is the slow growth of the tumor over the years, which can be verified if previous films are available. This growth might suggest malignancy except for its extremely slow rate. Heterotopic bone marrow must be differentiated from other posterior mediastinal tumors more commonly encountered, such as neurogenic tumors, lymphomas, aneurysms, and mesenchymal tumors. Neurogenic tumors, the type most frequently found in this location, are usually unilateral. Lymphomas are most often found in proximity to the hilum of the lung. An aortic aneurysm may present as a paraspinal mass, as was reported by Vaughan et al.<sup>13</sup> in 1955. However, erosion of vertebrae, intrinsic pulsation, and arteriographic studies will differentiate it from bone

\* Reference 16 came to our attention since this paper was first submitted for publication.

marrow. Radiologic diagnosis alone, however, cannot be decisive, and must be supplemented by hematologic studies and biopsy.

The etiologic role of chronic hemolytic disease in the growth of heterotopic marrow deposits is uniformly accepted. There are few hematologic studies defining the precise type of hemolytic anemia which is present, owing to the paucity of cases where clinical studies have been made. Ask-Upmark's patient, a 70 year old female, had a lifelong history of jaundice with "crises," splenomegaly, a mean cell diameter of  $6.6 \mu\text{c.}$ , and reduced osmotic resistance. Spherocytosis was not mentioned. A diagnosis of acholuric jaundice was made. The clinical findings were compatible with hereditary spherocytosis. Paraf's case 1 was a 71 year old female with a history of "crises" and increased osmotic fragility, but spherocytosis was lacking. Hereditary nonspherocytic anemia as described by Crosby was considered, but the history and the laboratory tests strongly suggested hereditary spherocytosis. Case 2 was typical of spherocytic hemolytic icterus. Handford's two cases, both males, showed nonspherocytic hemolytic anemia in one, and spherocytic hemolytic anemia in the other. In the case reported above, the history of jaundice, anemia, radiochromium studies showing defective erythrocytes and spherocytosis were typical of hereditary spherocytosis.

A review of the hematologic data in these six cases shows that the hemolytic anemia may be either spherocytic or nonspherocytic. Hereditary features have been proved in some instances. No cases of the acquired type have been reported. The hemolytic stimulus most likely arises from a congenital disease, or one acquired early in life, in order to produce tumors of sufficient size to be seen on the x-ray films. This is substantiated by the fact that the average age at diagnosis, either by autopsy or clinically in the cases reported to date, has been 65 years.

The diagnosis of mediastinal bone-marrow tumors, as has been mentioned, cannot be made decisively by the x-ray film, even though these tumors have radiologic characteristics which are very significant. The finding of a chronic hemolytic state, usually hereditary spherocytosis, increases the likelihood of a correct diagnosis. However, positive tissue identification can be obtained only by thoracotomy, with excision of the tumor, incisional biopsy, or needle biopsy. The latter method is preferred in order to avoid excessive hemorrhage.

The tissue genesis of heterotopic marrow has been an intriguing subject for speculation by all writers on this subject. Two separate theories of origin have been selected by Ask-Upmark to explain the diverse locations in which marrow masses are found. The first—or autochthonous—theory derives from the investigations of Petri.<sup>14</sup> He described proliferating hematopoietic foci in normal newborns in the retroperitoneal fat, and the fat of the breasts, groins, palms, soles, and broad ligaments. Remnants of these foci in the retroperitoneal region, if they retained their hematopoietic potential, could, under the stimulus of a longstanding hemolytic process, proliferate and form tumor masses of marrow such as have been described in the hilum of the kidney, hollow of the sacrum, and other abdominal locations. Such hematopoietic fat cannot explain the origin of mediastinal marrow tumors, for the latter are never found in the fat tissue of the mediastinum, but in the paravertebral area, which is normally devoid of fat. Furthermore, the tumors are often segmentally distributed alongside the

vertebrae, and are always in the posterior-inferior mediastinum. To explain this paraspinal localization, Ask-Upmark has drawn on the work of Cone,<sup>15</sup> whose investigations showed bone marrow filling the intercostal veins in 68 cases out of 250 necropsies. He felt that passive congestion or dyspnea assisted in the production of this phenomenon, and that some "change in the blood is a prerequisite." He thought that where veins and bone matrix were exposed together, changes in pressure in the veins could assist in the transference of marrow from bone to vein. Cone did not mention hyperplastic marrow or a hemolytic process, but these conditions would meet his requirement of a "change in the blood." The constant localization of these marrow tumors below the sixth thoracic vertebrae is explained, according to Ask-Upmark, by impairment in venous circulation owing to a watershed phenomenon at this level created by the two patterns of respiration—thoracic and abdominal. He summarizes his views on the development of mediastinal heterotopic marrow deposits as follows: "In other words, the primary factor seems to be embolic or metastatic displacement of bone marrow through the intercostal veins, facilitated by the condition of the marrow; the secondary factor will be the compensatory enlargement of the new dominion of bone marrow induced by the drain of hemolysis. This assumption being granted, it should be emphasized that only a demand of long duration is likely to further the evolution just outlined." A careful microscopic examination of all intercostal veins in the paraspinal areas of localization in cases of longstanding hemolytic disease might provide direct evidence for this theory.

The obvious rarity of intrathoracic bone marrow tumors deserves brief comment. In the last 15 years, many large series of cases of mediastinal tumors have been published, and in none has there appeared an instance of ectopic bone marrow classified as such. It is possible that these tumors are included in the group of unclassified cases—yet the histologic characteristics of bone marrow are so easily recognized that proper classification should be easy. This situation may stem from the relative rarity of chronic hemolytic disease itself. A more cogent reason is that chronic hemolytic disease, especially hereditary spherocytosis, is usually diagnosed early in life and arrested by splenectomy before heterotopic marrow can grow. Only in rare instances do cases of this type reach middle age undetected and untreated.

#### SUMMARY

Heterotopic bone marrow can produce a slowly growing paraspinal inferior mediastinal mass which may be bilateral or even somewhat segmental. Clinical evidence of chronic hemolytic disease, associated with such a mass, should lead to consideration of ectopic bone marrow as the explanation of the tumor. The diagnosis may be confirmed by needle biopsy or thoracotomy. This tumor does not produce symptoms, and is a manifestation of compensatory extramedullary hematopoiesis. Surgical excision is not advised.

#### SUMMARIO IN INTERLINGUA

Tumores intrathoracic de heterotopie medulla ossee se trova solmente in adultos con morbo hemolytic de duration prolongate. Iste tumores se trova uni- o bilateral-

mente in situs in le mediastino postero-inferior. Lor dimensiones varia con diametros de inter 2 e 6,5 cm. In le visualisation roentgenographic illos simula tumores mediastinal.

Es describite le caso de un masculo de 50 annos de etate con chronic anemia hemolytic e spherocytosis. Nulle base hereditari esseva demonstrabile. Nulle symptomas esseva presente que poteva esser attribuite al anemia o al systema respiratori. Le roentgenographia thoracic monstrava le presentia de un grande e lentamente crescente tumor dextero-paraspinal. Le diagnose esseva facite per thoracotomia e excision. Le examine microscopic monstrava que le tumor consisteva de medulla ossee. Subsequentemente le patiente se trovava in bon stato de sanitate durante un observate periodo de cinque annos, sin ulla alteration in le processo hemolytic. Splenectomy esseva refusate.

Iste caso pare esser le dece-quinte de su typo a trovar in le litteratura e le secunde in que le diagnose esseva establite durante le vita del patiente. Es signalate le reportos de Ask-Upmark e Paraf. Le prime de iste duo autores summarisa le disveloppamento de tal tumores in le sequepte terminos: "Il pare que le factor primari es un displaciamento embolic o metastatic de medulla ossee via le venas intercostal. Iste processo es promovite per le condition hyperplastic del medulla. Le factor que contribue secundarimente es allora le allargamento compensatori del nove area de medulla ossee que es inducite per le consumo del hemolyse. Si iste premissas es acceptate, il debe esser notate que solmente le demandas de un consumo de longe duration supporta le probabilitate del justemente delineate evolution."

Tumores de iste genere produce nulle symptomas. Illos es considerate como un manifestation de hematopoiese extramedullari. Per consequente, lor excision non pote esser recommendate.

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### CHRONIC LYMPHATIC LEUKEMIA AND MULTIPLE MYELOMA IN THE SAME PATIENT \*

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THE close relationship which seems to exist between lymphocytes and plasma cells has recently been the subject of much discussion.<sup>1, 2</sup> The frequent occurrence of apparently identical serum protein abnormalities in patients with malignant lymphoma, lymphatic leukemia and multiple myeloma, as demonstrated by paper electrophoresis, has been felt to be of particular significance. The consensus seems to be that plasma cells probably represent transitional forms of lymphocytes, as had been suggested by the work of Sundberg<sup>3</sup> and others,<sup>4</sup> and that both are capable of synthesizing abnormal serum proteins.

Although serum proteins of the myeloma type have occasionally been reported in patients with chronic lymphatic leukemia, as far as we have been able to determine no case has yet been described where there was clear-cut histologic evidence of both lymphatic leukemia and multiple myeloma occurring simultaneously in the same patient.<sup>5</sup> Such a case is here presented.

#### CASE REPORT

A 72 year old Portuguese male was first seen on April 23, 1956, complaining of a 10-pound weight loss over the previous nine months, and a painful mass in the left upper quadrant of about two months' duration. He had been quite well all his life except for mild hypertension. There was no history of exposure to toxic substances.

Physical examination revealed no significant abnormalities except a blood pressure of 170/88 mm. of Hg, a few small, firm lymph nodes in the left supraclavicular space, and an enlarged, slightly tender spleen extending 6 cm. below the left costal margin.

Laboratory determinations were as follows: white blood count, 103,600 per cubic millimeter, of which 99% were mature lymphocytes (figure 1); hematocrit, 32.7%; platelet count, 122,000 per cubic millimeter; nonprotein nitrogen, 39 mg. per 100 c.c. An attempt to obtain a specimen of bone marrow by needle aspiration was unsuccessful.

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A diagnosis of chronic lymphatic leukemia was made and treatment given in the form of x-ray to the spleen, 330 r in divided doses over a period of four days.

On May 2, 1956, immediately after the completion of roentgen-ray therapy, the patient complained of pain over the anterior aspect of the right sixth rib. Examination of x-ray films showed an expansive, destructive lesion in the anterior end of the sixth rib with a linear dimension of about 6 cm. (figure 2). Skeletal survey films at that time showed no evidence of other bony lesions. A biopsy specimen from the rib lesion obtained on May 7, 1956, was identified histologically as plasma cell myeloma. The slides were reviewed by several pathologists, who concurred in this diagnosis.

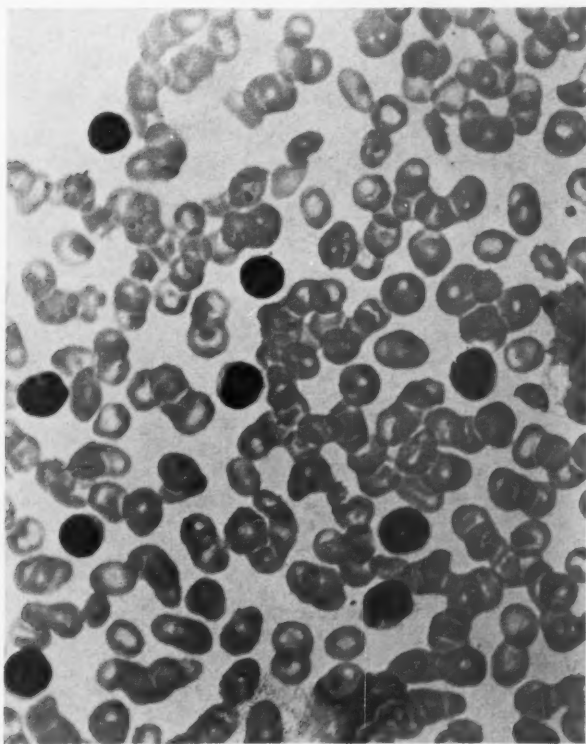


FIG. 1. Peripheral blood smear (Wright's stain) showing mature lymphocytes. Total white count, 103,600 per cubic millimeter with 99% mature lymphocytes.

On May 14, 1956, two weeks after irradiation of the spleen, the white blood cell count was 8,900 per cubic millimeter; hematocrit, 34.8%. The spleen had decreased in size to 4 cm. below the costal margin. At that time a serum protein determination revealed a level of 8.2 gm. per 100 c.c., with an A/G ratio of approximately one. The serum electrophoretic pattern was considered to be consistent with that of multiple myeloma. The patient felt quite well except for moderate pain over the right anterior chest.

There was little change until October 1, 1956, at which time the chest pain became more severe, and a palpable mass developed over the anterior sixth rib. The leukemic



FIG. 2. X-ray of the chest, showing an osteolytic lesion in the anterior end of the right sixth rib. Biopsy specimen revealed a dense mass of plasma cells characteristic of myeloma.

process seemed inactive, although the spleen had increased in size from 3 cm. to 8 cm. below the costal margin. The hematocrit was 38% and the white blood cell count was 44,600 per cubic millimeter.

The rib lesion was treated by x-ray therapy between October 4 and October 10, 1956, with 1,800 r. There was complete relief of pain.

A serum electrophoretic pattern obtained on October 9, 1956 (figure 3) again showed an increase in gamma globulin. The percentage distribution of protein components was as follows:

Albumin	24.6%
Globulin	
Alpha 1	2.6%
Alpha 2	6.3%
Beta	6.3%
Gamma	60.3%

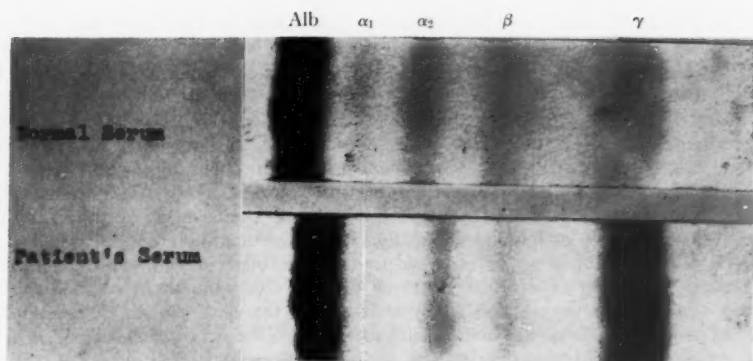


FIG. 3. Paper electrophoretic serum protein pattern of a patient with combined multiple myeloma and chronic lymphatic leukemia, compared with a normal pattern. Gamma globulin is greatly increased.



FIG. 4. X-ray of the cervical spine, showing partial collapse of the fifth cervical vertebra.

The patient felt fairly well until January, 1957, at which time there was obvious progression of disease. His neck was painful on flexion, and he had developed anorexia, weight loss, and ease of fatigability. The spleen had further increased in size and the liver was now palpable. The white blood cell count was 19,000 per cubic millimeter, with 87% lymphocytes, and the hematocrit was 26%. The total serum protein had risen to 15.5 gm. per 100 c.c., with an A/G ratio of 0.22. The electrophoretic pattern again showed a very evident increase in gamma globulin.

Skeletal roentgenograms on January 14, 1957, showed a large soft tissue mass associated with the area of destruction in the anterior portion of the right sixth rib, but now with evidence of some recalcification in the surrounding cortex. There were multiple tiny punctate areas of radiolucency in both upper femora and the ischia. There was narrowing of cervical vertebrae C5 and C6, with slight collapse of C5 (figure 4). On February 1, 1957, reexamination of the skull showed definite small, rounded areas of radiolucency which had not been visible on previous films. These were considered to be characteristic of multiple myeloma.

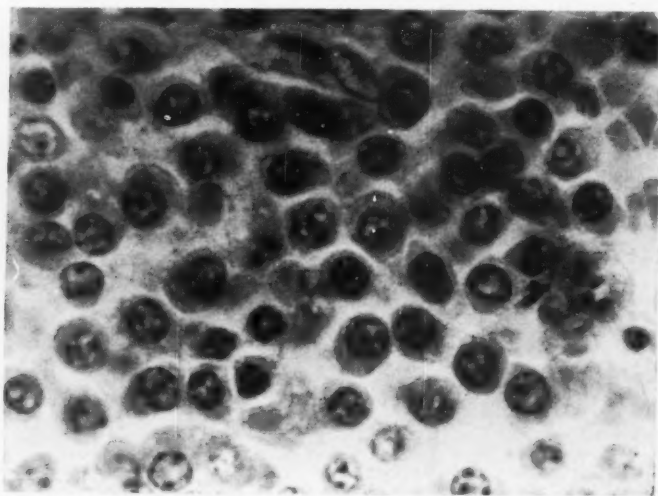


FIG. 5. Highly cellular bone marrow, showing masses of mature plasma cells.

The patient became progressively worse. A partial collapse of the right middle lobe and an elevated nonprotein nitrogen of 95 mg. per 100 c.c. developed, and the patient died on February 26, 1957.

*Necropsy Findings:* The body was that of a well developed, well nourished white male appearing somewhat younger than the stated age. Except for enlarged inguinal lymph nodes, the external examination showed no significant abnormality.

The heart weighed 490 gm. Sections of the myocardium showed no hemorrhage, inflammation or fibrosis. The wall of the left ventricle was hypertrophied, measuring 15 mm. in thickness. All valve leaflets were thin and pliable.

There were 500 c.c. of cloudy yellow fluid in the right pleural cavity, and none in the left. The lungs weighed 1,060 and 1,070 gm., respectively. There was patchy consolidation of all lobes, and microscopically the alveoli were filled with edema fluid and purulent exudate. There were two abscesses in the right upper lobe.

The liver weighed 1,550 gm. and grossly appeared to be normal. Histologic sections, however, showed considerably more than the usual numbers of lymphocytes in the portal areas.

The spleen weighed 480 gm. and was uniformly firm and dark red. Microscopically the architecture was obliterated by a diffuse infiltration of small, mature lymphocytes.

The kidneys weighed 140 and 150 gm. respectively. There was no gross abnormality, but microscopically there were dense collections of lymphocytes in both the cortex and the papillae.

There was generalized enlargement of lymph nodes. Sections of lymph nodes from many areas showed the architecture of all of these to be destroyed by dense infiltrations of mature lymphocytes, which in every case extended into the extracapsular adipose tissue.

The bone marrow (rib, sternum and vertebrae) was highly cellular and presented two distinct patterns. The greater part of the marrow consisted of hematopoietic myeloid tissue with interspersed fat cells. These areas contained a high proportion of small, mature lymphocytes. In addition, there were many scattered, discrete masses of rather uniform, closely packed mature plasma cells with minimal stroma and no associated fat cells (figure 5). Occasional mitotic figures were seen in these areas. There were no pertinent findings in other organs.

The principal pathologic diagnoses were:

1. Chronic lymphocytic leukemia involving lymph nodes, liver, spleen, kidneys, and bone marrow.
2. Multiple myeloma in vertebrae, sternum and rib.
3. Bronchopneumonia with abscesses.
4. Hypertrophy of left ventricular myocardium.

#### DISCUSSION

A case of combined multiple myeloma and chronic lymphatic leukemia is reported because it represents an unusual combination of diseases which has not been previously described. It also serves to focus further attention upon the hypothesis that plasma cells and lymphocytes are closely related, one perhaps being a transitional form of the other.

The presence of both multiple myeloma and lymphatic leukemia in this patient seems well established by the histologic findings. A biopsy specimen of the rib lesion, and specimens of bone marrow from the rib, sternum and vertebra subsequently obtained at autopsy, all exhibited discrete masses of closely packed plasma cells diagnostic of myeloma.

Sections of lymph node and spleen showed obliteration of the normal architecture and a diffuse infiltration by lymphocytes. This picture, together with the presence of large numbers of circulating lymphocytes (approximately 100,000 per cubic millimeter before the institution of x-ray therapy), is sufficient evidence to justify a diagnosis of lymphatic leukemia. While the lymphocytosis alone might be considered to be merely a manifestation of a nonspecific reaction to the underlying myelomatous process, a "leukemoid" reaction, the additional finding of loss of normal histologic pattern in the lymph nodes and spleen, with dense lymphocytic infiltration, places this unquestionably in the category of true lymphatic leukemia.

The origin of the abnormal serum proteins seems of especial interest since,

in accordance with the studies of others, these could be attributed either to plasma cells or to lymphocytes. The presence of large numbers of both types of cells in the same patient emphasizes further the interesting speculation that multiple myeloma may also be one of the several variants of the lymphomatous diseases.

#### SUMMARY

A case history of a patient with both chronic lymphatic leukemia and multiple myeloma is presented. This serves to emphasize further the hypothesis that plasma cells and lymphocytes may be closely related, and that multiple myeloma is perhaps one of the variants of the lymphomatous diseases.

#### SUMMARIO IN INTERLINGUA

Es reportate, in le interesse de un re-accentuation del intime relation que pare exister inter plasmocytos e lymphocytos, le caso de un patiente qui habeva concomitantemente myeloma multiple e chronic leucemia lymphatic.

Le caso es illo de un masculo de 72 annos de etate, con le gravamines initial de perdita de peso e un penose massa in le quadrante supero-sinistre del abdomine. Un diagnose de chronic leucemia lymphatic esseva facite super le base de generalisate lymphadenopathia e splenomegalia e un peripheric numeration leucocytic de 103.600 per millimetro cubic, representate a 99% per lymphocytos matur. A causa del presentia de anemia (con un hematocrite de 32,7%), le patiente esseva tractate con 330 r de local radios X al splen. Le responsa esseva bon. Intra duo septimanas le hematocrite monstrava un augmento a 34,8%; le splen habeva reduce su dimensiones; e le numeration leucocytic habeva descendite a 8.900 per millimetro cubic.

Brevemente post le tractamento, le patiente se plangeva de dolores in le region supra le thorace dextero-anterior, e un roentgenographia revelava le presentia de un expansive lesion destructive al termino anterior del sexte costa. Roentgenographias investigatori del skeleto esseva alteremente negative. Un specimen biopic ab le lesion costal esseva identificate histologicamente como myeloma plasmocytic. A iste tempore, le proteina total del sero esseva 8,2 g per 100 cm<sup>3</sup>. Le proportion de albumina a globulina esseva 1 a 1, e le configuration electrophoretic del sero esseva congrue con myeloma multiple. Le lesion costal deveniva de plus in plus dolorose, e un massa palpabile se disveloppava. Tamen, therapia local a 1.800 r de radios X resultava in le complete alleviamento del symptomatas.

Le stato del patiente se deteriorava progressivamente. Le splen e le hepate augmentava lor dimensiones, e le patiente disveloppava anorexia e perdita de peso. Le valor del hematocrite descendeva a 26%. Le proteina total del sero montava a 15,5 per 100 cm<sup>3</sup>, con un proportion de albumina a globulina de 0,22. Multiple micre areas punctate de radiolucencia appareva in expositiones del cranio, del femores, e del pelve. Esseva etiam notate un leve grado de colapso del quinte vertebra cervical. Esseva opiniate que iste alterationes esseva characteristic de myeloma multiple. Finalmente le patiente moriva de bronchopneumonia.

Le major puntos del diagnose, super le base del constatationes necroptic, esseva chronic leucemia lymphatic, myeloma multiple, e bronchopneumonia. Le medulla ossee esseva de interesse particular. Illo esseva altamente cellular e exhibiva duo distincte configurationes. Le un consisteva de myeloide tissu hematopoietic que contineva un alte proportion de micre lymphocytos matur. Le altere consisteva de discrete massas de satis uniforme, compingitissime plasmocytos matur. Sectiones de nodos lymphatic ab varie areas revelava un destruction del architectura normal per dense infiltrationos de lymphocytos matur le quales, in omne casos, se extendeva in le tissu extracapsular.



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**ANDROGEN THERAPY FOR REFRACTORY ANEMIA: REPORT OF A CASE ASSOCIATED WITH THYMOMA \***

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PATIENTS receiving androgen therapy for metastatic carcinoma of the breast have been observed to show increased erythropoietic activity of a degree which may raise subnormal blood counts to normal or polycythemic levels. Bone marrow examination in these patients revealed increased erythropoietic activity, although no blood transfusions or hematinics were administered. The medication employed has been testosterone propionate, given intramuscularly in doses of 50 to 100 mg. three times a week, or in equivalent oral doses. The phenomenon occurs in 16 to 64% of the patients treated. Why some patients respond and some do not is not known. The concomitant administration of cortisone augments the erythropoietic effect.<sup>1</sup>

Because of the possibilities of stimulating erythroid activity, androgenic hormone therapy has been utilized in other conditions associated with idiopathic erythroid hypoplasia. There have been good results from the use of testosterone in a few cases of refractory anemia associated with osteoporosis, hypogonadism, diabetes mellitus and chronic glomerulonephritis.<sup>1</sup>

Control of the anemia of castrated male animals by androgen therapy has been reported.<sup>2</sup> The administration of androgens to normal animals has resulted in increased reticulocytosis and elevation of the blood hemoglobin and red blood count,<sup>3</sup> and is definitely a stimulus to erythropoiesis.<sup>4</sup> It is significant that hypochromic anemia is much more common in older women than in older men, and that boys past puberty have higher hemoglobin levels than do girls in the same age group.<sup>5</sup> There is evidence that the most feminine women have the lowest hemoglobin values, and that the most masculine, hard-driving type of man tends toward plethora and high hemoglobin values.<sup>6</sup> Hypopituitarism has been reported with anemia which was responsive to testosterone.<sup>7</sup> Eunuchoid

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men are reported to run low hemoglobin levels.<sup>8</sup> Erythroblastic hypoplasia associated with thymic tumors has been reported with and without myasthenia gravis. Of six cases reported by Thompson and Winebaum,<sup>9</sup> two were cured by thymectomy. Other cases of anemia and thymoma have been associated with hypoplastic bone marrow.<sup>10, 11</sup> There may be associated agammaglobulinemia, thrombocytopenia and splenomegaly.

In the following case, refractory anemia with decreased erythropoietic activity and thymoma did not respond to cortisone therapy, removal of the thymic tumor, or splenectomy, but did enter a remission (which had lasted one year at the time of this report) as a result of intensive androgen therapy. No similar case has yet appeared in the medical literature.

#### CASE REPORT

A 69 year old white male theatre manager first sought medical advice on September 21, 1955, with the complaint that for about two months he had noted that walking made him short of breath. He had also noted in the same interval that his leg muscles cramped when he went to bed at night. No other symptoms referable to any other system could be elicited except that he had been going to a dermatologist for "ringworm" of the skin of the perineal area. The dermatologist had noticed his pallor and urged him to seek general medical advice because of his anemic appearance.

There was no significant personal or family history. The patient had had a hemorrhoidectomy 10 years previously, without any complications.

He appeared to be an adequately nourished man, and in spite of his marked pallor to be about 10 years younger than his stated age of 69. His blood pressure was 110/74 mm. of Hg; pulse, 82 and regular. There was a chronic tinea dermatitis of the ankles and perineum. His tongue was smooth and pale but showed no changes compatible with a deficiency syndrome.

The blood count showed: hemoglobin, 4.2 gm. per 100 c.c. (27%); erythrocytes, 1,280,000 per cubic millimeter; leukocytes, 6,950, with 3% staphs, 49% segmented neutrophils, 46% lymphocytes; 2% eosinophils; 215,000 platelets; 0.1% reticulocytes; hematocrit, 50 mm. The mean corpuscular hemoglobin was 32; mean corpuscular volume, 117; mean corpuscular hemoglobin concentration, 28. The blood serology was negative. The urinalysis was normal, specific gravity being 1.020. There was no occult blood in the stool. There were no abnormalities of the serum proteins, and no evidence of auto-agglutinins. The electrocardiogram was normal. The gastric analysis was normal. A bone marrow puncture showed a myeloid-erythroid ratio of 12:1. The rare cells of the erythroid series present appeared to be maturing normally. The myeloid and megakaryocyte series also appeared to be maturing normally. Many lymphocytes were present, accounting for about two thirds of the white cells. The bone marrow appearance was that of bone marrow depression, possibly resulting from some intoxication. The x-rays and films of the upper digestive tract were normal, and the barium enema was normal. The x-ray and fluoroscopy of the chest showed a large ovoid nodular mass, approximately  $8\frac{1}{2} \times 10\frac{1}{2}$  cm. in size, in the midline of the body, extending to the left and along the left heart border. There was no evidence of active pulmonary infiltration. The exact nature of the lesion could not be determined (figure 1). Because the shadow appeared to pulsate, an arteriogram was done, which did not show aortic aneurysm.

The possibility of thymoma associated with refractory anemia was recognized, and thymectomy was recommended to the patient, but he preferred to postpone it. A course of cortisone was therefore started on October 11, 1955, with an initial dose of 300 mg. and gradual reduction to 200 mg. daily, with the usual low sodium diet and potassium supplement. The patient was also given a cobalt and iron preparation

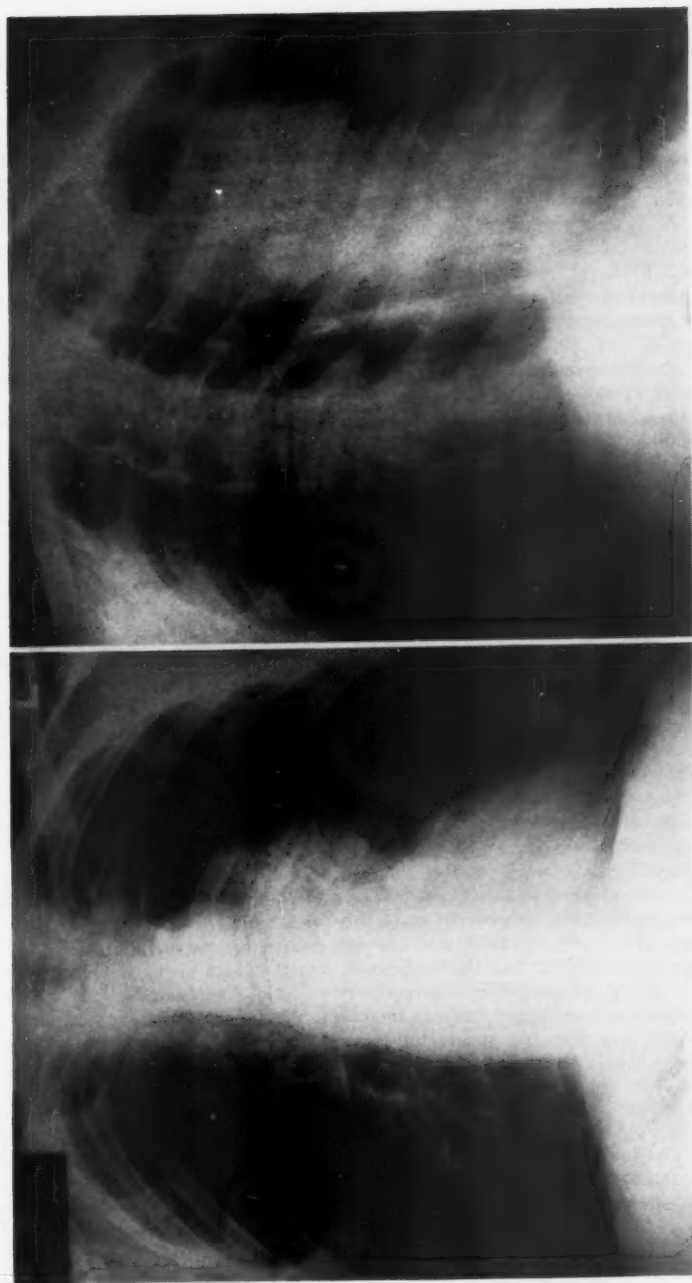


FIG. 1. *A*, Posteroanterior, and *B*, left lateral roentgenogram of chest showing left hilar mass (thymoma) in anterior superior mediastinum.

(Roncovite) and a polyvitamin. Prior to the institution of cortisone therapy he received several transfusions, raising his hemoglobin to 10.7 gm. per 100 c.c., and the erythrocytes to 3,090,000 per cubic millimeter. The patient then went to the Mayo Clinic, where his case was evaluated, with about the same results. Because of the chest x-ray evidence of a hilar mass, a thoracotomy was done and a well circumscribed lesion in the anterior mediastinum was removed.<sup>12</sup> The pathologist's report was: small cell (thymocytic) type of thymoma. The abdomen was explored at the same time and the spleen was normal, as were the stomach, pancreas and liver. The gall-bladder was distended and not easily compressible, but no stones were palpable. No other masses or lymphadenopathy was demonstrable. The patient received several transfusions before and after surgery, which was performed on December 2, 1955.

No other treatment was given, in the hope that the blood regeneration would follow the thymectomy.

On January 11, 1956, approximately five weeks following the surgical operation, the anemia had progressed to 6.6 gm. of hemoglobin per 100 c.c., 2,350,000 per cubic millimeter of erythrocytes. Prednisone, 25 mg. a day, was therefore started. At the same time, cobalt and iron (Roncovite) was reinstituted. The blood count continued to fall, and the patient was given 3,500 c.c. of blood, 500 to 1,000 c.c. at a time, over a period of the next three weeks. In February, 1956, he received several injections of vitamin B<sub>12</sub>, although there was no particular indication therefor, to see what effect it might have. It had none. He continued to receive periodic transfusions, prednisone, and cobalt and iron. From February through June, 1956, a program of periodic transfusions and the medications mentioned above were continued. There was still no sign of blood regeneration. Reticulocytes remained below 0.1%.

The patient returned to the Mayo Clinic, and on July 21, 1956, a splenectomy and a cholecystectomy were performed, the latter because of the presence of gall-stones. A skin lesion was removed from one foot. The cytologic diagnosis was Kaposi's hemorrhagic sarcoma. On July 23 the hemoglobin was 10 gm. per 100 c.c.; on July 27 (the sixth postoperative day) it was 9 gm. per 100 c.c.; August 7 it was 9.6 gm. per 100 c.c. There was no evidence of reticulocytosis postoperatively. The patient received no medication other than the polyvitamin, except for 500 c.c. of blood on August 22. The blood count continued to drop, and the hematologic situation remained the same from August, 1956, until May, 1957. During this interval the patient received a blood transfusion of 500 c.c. every two to three weeks.

On May 29, 1957, with the reticulocyte count at 0.1%, hemoglobin at 6.6 gm. per 100 c.c., and erythrocytes at 2,290,000 per cubic millimeter, oral androgen therapy was started in the form of methyltestosterone, 50 mg. daily. On the same date the patient was given 500 c.c. of blood. In the course of one month there was no hematologic improvement, and the medication was therefore changed to testosterone propionate, 50 mg. intramuscularly three times a week. On June 26, 1957, although the hemoglobin and red count had not improved, the reticulocytes were estimated at 0.3%. There was slow but steady improvement, with the hemoglobin rising over a period of a month to 7.8 gm. per 100 c.c., and erythrocytes to 2,270,000 per cubic millimeter. On August 13, 1957, the reticulocyte count was 2.5%, having been as high as 4.9% on July 24, 1957 (figure 2). The blood count continued to improve, reaching 11.6 gm. hemoglobin per 100 c.c. and 3,210,000 erythrocytes per cubic millimeter on October 1, 1957. By November 22, 1957, hemoglobin was 13.4 gm. per 100 c.c., and erythrocytes were 3,600,000 per cubic millimeter. The leukocytes remained between 8,000 and 10,000, with no particular change in differential. On December 11, 1957, the therapy was discontinued. On that date the hemoglobin was 14 gm. per 100 c.c., and erythrocytes were 4,040,000 per cubic millimeter. Over a period of six months there was only a slight drop of the blood count, hemoglobin

being 12.6 gm. per 100 c.c., and erythrocytes, 4,500,000 per cubic millimeter on June 24, 1958. On November 7, 1958, the blood count was 11.2 gm. hemoglobin per 100 c.c., erythrocytes, 3,870,000 per cubic millimeter, leukocytes, 7,850, with 7 staphs, 54 segmented neutrophils, 37 lymphocytes and 2 eosinophils. An almost identical count was done on December 28 1958 (figure 2).

In July, 1957, at which time the regeneration of the patient's blood seemed to be at its height, he developed idiopathic effusion of the left knee joint. This was aspirated and treated with one intra-articular injection of hydrocortisone, with complete recovery.

At the time of the last blood count, one year after all treatment had ceased, the patient was feeling well and had no complaints.

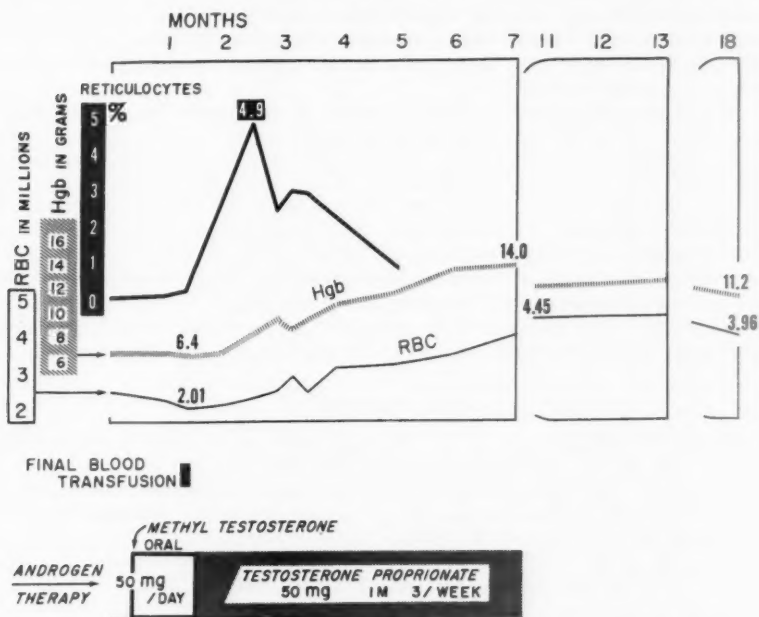


FIG. 2. Result of androgen hormone therapy on level of blood reticulocytes, erythrocytes and hemoglobin.

#### SUMMARY AND CONCLUSIONS

This case demonstrates two points of considerable clinical interest. The first point is the relationship of benign thymoma and refractory anemia, possibly of some common genesis. This aspect of the problem was thoroughly reviewed by Bayrd and Bernatz,<sup>12</sup> of the Mayo Clinic, in a recent contribution in which this patient was one of two with thymoma and refractory anemia that they have added to the 12 cases previously described by various authors.

The second point is the therapeutic value, under special circumstances, of androgen therapy for erythroid hypoplasia. The hematologic remission that so far has lasted a year is noteworthy and has not been reported previously.

This paper is in no way a recommendation for the indiscriminate use of androgenic hormone therapy in anemia of uncertain etiology.

## SUMMARIO IN INTERLINGUA

Le uso de androgeno in le therapia de metastatic carcinoma mammari resulta a vices in un augmento del activitate erythropoietic in le absentia de un simultanee administration de transfusiones de sanguine o de hematinicos. A causa de isto, hormones androgene ha essite utilisate in altere conditiones associate con idiopathic hypoplasia erythroide. In certe tal casos, le syndrome in question comprendeva osteoporosis, hypogonadismo, diabete mellite, e glomerulonephritis chronic. Si androgenos es administrate a animales normal, augmentos del reticulocytosis e etiam augmentos del nivello de hemoglobina sanguinee e del numeration erythrocytic ha essite observate. Il existe reportos del observation que masculos eunuchoides ha basse nivellos de hemoglobina, durante que le plus aggressive e le plus viril typo de masculo tende a esser plethoric. Anemia hypochromic es plus commun in feminas de etate avantiata que in homines de etate avantiata, e adolescentes de sexo masculine qui ha passate lor pubertate ha plus alte nivellos de hemoglobina que adolescentes de sexo feminin a correspondente etates.

Hypoplasia erythroblastic ha essite reportate in association con tumores thymic, e in un numero de casos illo esseva curate per thymectomy.

Es reportate un caso de anemia refractori con reducite activitate erythropoietic del medulla ossee, associate con thymoma. Nulle melioration clinic resultava del therapia a cortisona, del excision del tumor thymic, e del effectuation de splenectomy. Un remission—perdurante, a iste tempore, de post plus que un anno—ha resultate de un curso intense de therapia androgenic. Specificamente le therapia consisteva de propionato de testosterona administrate in doses de 50 mg per via intramuscular tres vices per septimana durante approximativemente sex menses.

Nulle simile caso ha previamente esse reportate, ben que un total de 14 casos de thymoma con anemia refractori se trova discutate in le litteratura medical.

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**Q FEVER ASSOCIATED WITH GRANULOMATOUS HEPATITIS \***

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Q FEVER is an acute febrile disease with systemic manifestations, caused by the rickettsia *Coxiella burnetii*, and usually transmitted by inhalation, without an intermediate vector. It has now been reported throughout the world, and is endemic in many parts of the United States, especially California. Emphasis is usually placed on the pulmonary aspects of the disease; however, we are reporting three cases of Q fever that came under our care during a recent epidemic in Alameda County, each presenting as hepatitis with inconspicuous or absent pulmonary findings. Liver biopsy in all three cases demonstrated a diffuse granulomatous process with multinucleated giant cells. Diffuse tuberculosis was strongly considered until serologic studies confirmed the diagnosis of Q fever.

In the original 1937 report describing Q fever as a new clinical entity, Derrick<sup>1</sup> noted anemia, icterus and fever in one of his nine cases, although fever and respiratory symptoms were more common.

The most common clinical features reported by Clark et al.<sup>2</sup> in 1951 in a study of 180 cases were fever, chills, malaise and headache. This symptom complex occurred in more than three fourths of the patients. Cough or chest pain was present in only 34%. Hepatomegaly or tenderness over the liver area was noted in 18% of the cases, and icterus was observed in 5%. Ordinarily, evidence of hepatic involvement became apparent in the second or third week of illness, and most of the patients with such evidence had a prolonged clinical course. In the Clark study, cephalin flocculation and thymol turbidity were tested in only two cases but were abnormal in both. One case suffered severe epistaxis, and the prothrombin concentration was found to be 0%.

The seriously ill patients of the Clark study showed a generally poor response to chlortetracycline, although in most investigations, both clinical and experimental, oxytetracycline, chlortetracycline and chloramphenicol have had a specific therapeutic effect. Patients usually became afebrile in from 24 to 48 hours on these drugs.

Few deaths have been attributed to Q fever; only a half-dozen fatalities are reported in the literature.<sup>4</sup> Autopsies were performed on four of these, and specific abnormal findings were limited largely to the lungs, with a consolidated bronchopneumonia as the major finding, although in one case foci of hypoplastic bone marrow were reported. No pathologic changes in the liver were recorded.

Recent advances in percutaneous liver biopsy technics have been accompanied by reports of abnormal liver specimens obtained from patients with Q fever manifesting clinical hepatitis. Gerstl et al.<sup>5</sup> reported four Q fever patients with biopsy findings of focal hepatitis, characterized by inflammatory cell infiltration and coccoid intracytoplasmic inclusions; no true granulomata containing multi-

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nucleated giant cells were found. This group also noted the discrepancy between liver function test results and the biopsy findings.

In 1958 Shuman and Galloway<sup>6</sup> reported another case of Q fever with liver involvement where liver biopsy showed focal and scattered infiltrations of polymorphonuclear leukocytes, lymphocytes and macrophages, although the biopsy was taken more than six weeks after the onset of the illness, and about one month after the last febrile day. This patient had only a transient response to treatment with tetracycline, but became afebrile and remained so on chloramphenicol.

Another case of Q fever with involvement of the liver manifested by abnormalities in tests of liver function was reported by Hurwitz and McLaughlin<sup>7</sup> in 1959, but no biopsy evidence was obtained.

Our report consists of three cases of Q fever, proved by serologic tests, who presented with liver involvement as the primary finding. Liver biopsy in the acute phase of the illness produced specimens showing a diffuse granulomatous process with multinucleated giant cells. The specimens were initially interpreted as probable miliary tuberculosis. Each of the cases also had abnormalities of tests of liver function, and all had a prompt response to administration of chloramphenicol.

#### CASE REPORTS

*Case 1.* A 44 year old white male apartment house caretaker was admitted to Highland-Alameda County Hospital on May 29, 1959. Seven days prior to admission he had had an abrupt onset of chills, fever, headache, anorexia and malaise. Twenty-four hours later he developed a continuous dull ache in the right upper quadrant of his abdomen, unrelated to food intake and associated with slight nausea. He lost his taste for cigarettes, having previously smoked a package per day. The patient lived in poor surroundings but denied contact with raw milk, contaminated water or animals. There was no history of injections or drug intake. The only other member of his household was his wife, who was in good health. The past history was noncontributory.

Physical examination revealed an apprehensive middle aged white male complaining of abdominal pain. Blood pressure was 112/72 mm. of Hg; pulse, 100; respiration, 20; temperature, 104° F. The mucous membranes were dry. The abdomen was tender in the epigastrium and right upper quadrant, but no organs or masses were definitely palpable. Bowel sounds were normal. The rest of the physical examination was unremarkable.

*Laboratory Work and Hospital Course:* Packed cell volume, 38%; white blood cell count, 6,750, with 64% polymorphonuclears, 16% bands, 1% basophils, 16% lymphocytes and 3% monocytes. Urinalysis was negative. Admission chest x-ray, flat plate of the abdomen, upper gastrointestinal series, gall-bladder series and excretory urograms were all negative. A repeat chest x-ray three days after admission showed a diffuse mottling in the right lung consistent with an early bronchopneumonia. A later chest x-ray showed complete clearing. Although no physical findings were associated with this x-ray picture, there was a slight, unproductive cough.

Three blood cultures prior to antibiotic treatment were sterile. Stool and urine cultures were negative for typhoid organisms, and agglutination studies for typhoid and paratyphoid were negative on two occasions. Agglutinations for Brucella and a Paul-Bunnell heterophil titer were both negative. The result of the serologic test for syphilis as performed with the Venereal Disease Research Laboratory (VDRL) antigen was negative. Three examinations of the stool for ova and parasites were negative. The blood urea nitrogen was 12 mg.%, and the serum

amylase was 46 and 106 Somogyi units. Repeat blood counts showed no appreciable change from the admission count.

The initial treatment consisted of gastric suction and intravenous fluids, but there was little change in the patient's symptoms. He became hyponatremic, probably due to overadministration of hypotonic solutions. During the correction of his electrolyte imbalance he became psychotic, and had auditory and visual hallucinations for two days. A lumbar puncture revealed a clear spinal fluid and normal pressure.

After the initial blood, stool and urine cultures the patient was started empirically on intravenous chloramphenicol, 2 gm. daily, and later 2 gm. a day by mouth. Chloramphenicol was given from May 30 through June 15. Two days after administration of chloramphenicol was begun his fever began to lyse, and over a nine-day period returned to normal. During this time his symptoms subsided completely and his appetite returned (table 1).

TABLE 1

Approximate Day of Illness	Case 1				Case 2			Case 3		
	7	17	19	24	16	26	46	31	39	54
Icterus index		4		4	16	4	3	18	10	6
Alkaline phosphatase (King-Armstrong units)	7	40	50	32		20	14	25	25	20
Thymol turbidity	1	3.5		5.5	16.5	18.6	11.5	10.8	12.6	12.5
Cephalin flocculation	2+			4+	4+	4+	4+	4+	4+	4+
Total protein	5.8	6.2		6.7	6.8	6.7	7.2	6.5		
Albumin	2.6	3.2		3.5	2.3	2.3	3.1	2.6		
Globulin	3.2	3.0		3.2	4.5	4.4	4.1	3.9		
Prothrombin time (Per cent of normal)	100%				57%			50%	90%	
B.S.P. retention					20%					
Liver biopsy	On 20th day of illness				On 22nd day of illness			On 35th day of illness		

Q fever agglutination studies were done by the California State Laboratory. On June 13, the twenty-fifth day of illness, the titer was 1:128; on June 23, 1:512. A Vim-Silverman needle biopsy of the liver revealed scattered granulomata with multinucleated giant cells (figures 1, 2).

*Case 2.* A 36 year old white female came to Highland-Alameda County Hospital on June 4, 1959, complaining of chills, fever, headache, nausea, vomiting and malaise for two weeks. She had been in good health, and denied exposure to jaundiced individuals, recent injections or drug intake of any kind. There was no history of alcoholism.

Admission physical examination revealed slightly icteric sclerae, a few spider angiomas on the shoulders, and slight tenderness to palpation in the right upper quadrant of the abdomen. The liver and spleen were not palpably enlarged. The remainder of the physical examination was unremarkable.

*Laboratory Results and Course:* Packed cell volume, 36.5%; white blood cell count, 11,500, with 64% segmented neutrophils, 10% bands, 2% metamyelocytes, 22% lymphocytes and 2% eosinophils. Repeat blood counts showed a drop in the hematocrit to 30, where it remained. The white blood cell count returned toward

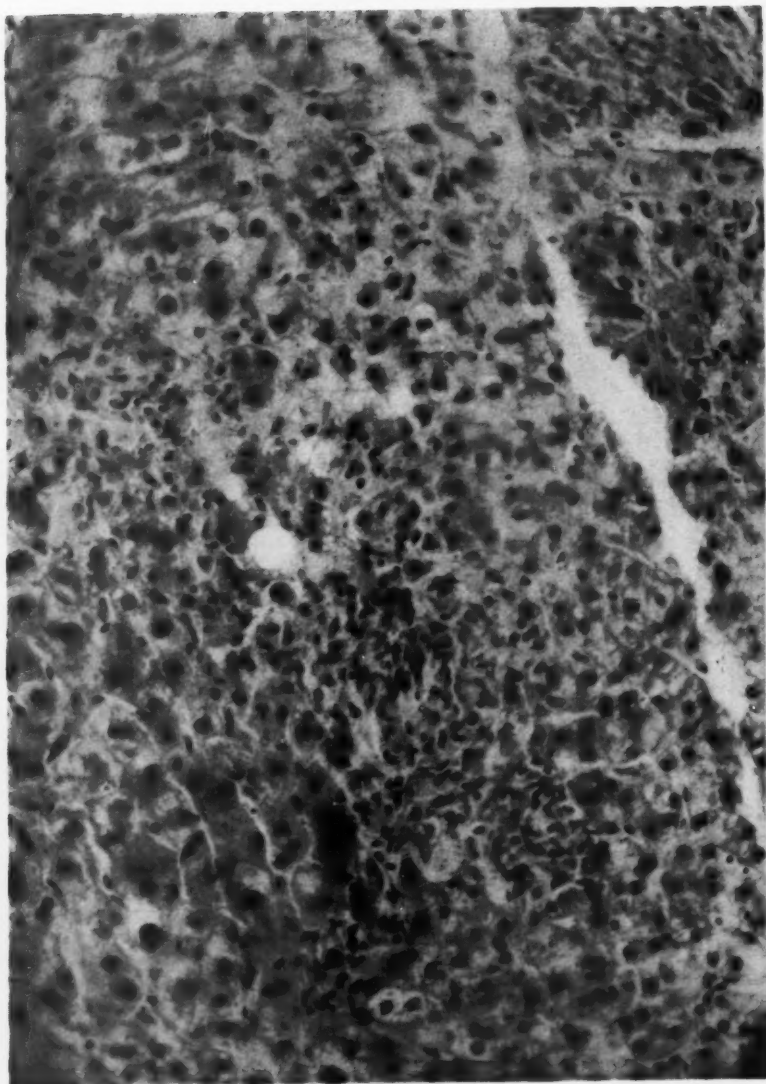


FIG. 1. *Case 1.* Liver biopsy, June 11, 1959. Small granulomatous foci scattered throughout the liver parenchyma without relation to portal areas. The foci consist of a few polymorphonuclears, a few eosinophils and a few mononuclear phagocytes. (Photomicrograph  $\times 375$ .)

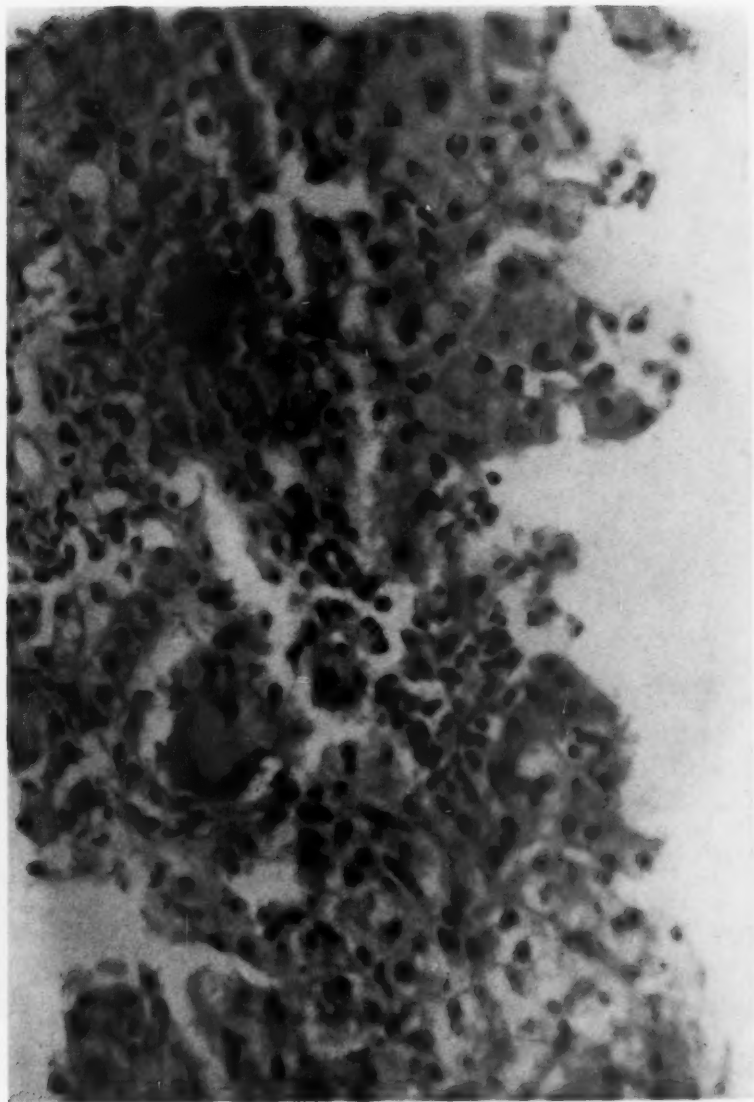


FIG. 2. Case 1. June 11, 1959. Higher magnification, showing a multinucleated giant cell. (Photomicrograph  $\times 475$ )

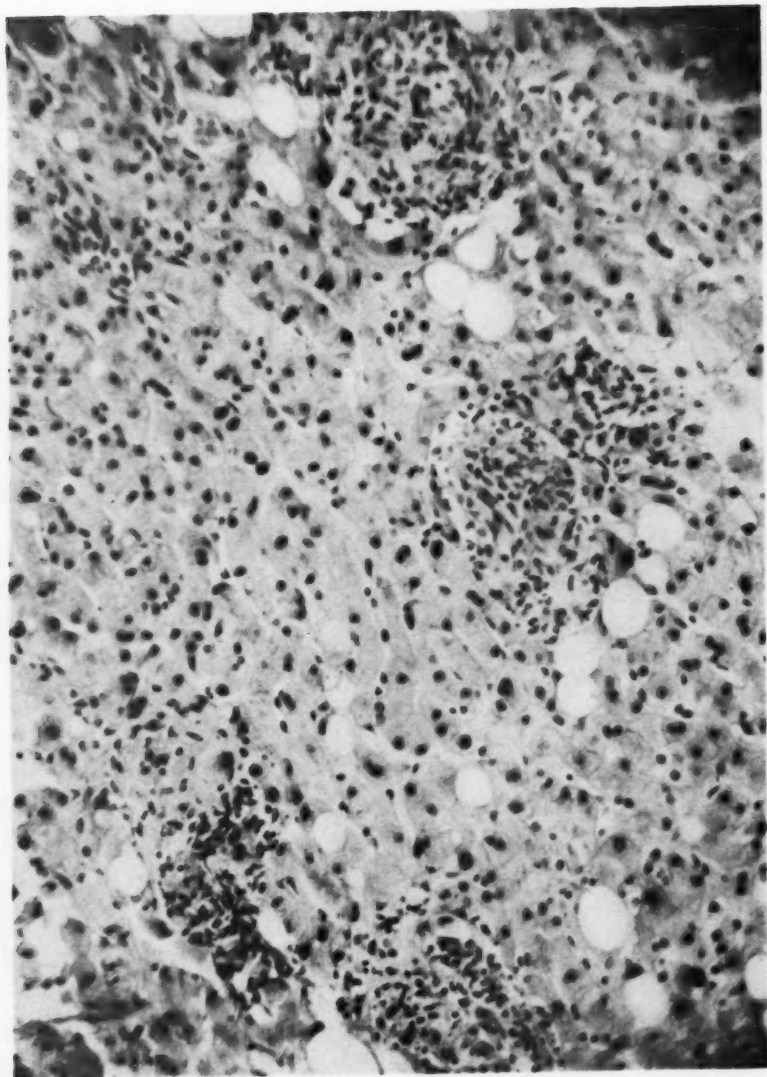


FIG. 3. Case 2. Liver biopsy. Granulomatous foci scattered throughout liver parenchyma. Many of the granulomata have an epithelioid character and contain multinucleated giant cells. The foci were unrelated to the portal areas. (Photomicrograph  $\times 375$ .)



normal and maintained a slight left shift. Chest x-ray was normal except for a slight elevation of the right diaphragm. X-ray of the kidneys, ureters and bladder was negative. Blood urea nitrogen was 10 mg.% Agglutination studies for *Brucella* and heterophil antibodies were negative (table 1).

During the first two weeks of hospitalization the patient had chills and daily fever spikes to 103° F. Liver biopsy obtained on June 18, 1959, showed microscopic granulomata with multinucleated giant cells (figures 3, 4). Culture of the liver biopsy material was sterile, and guinea pig inoculation was negative.

Chloramphenicol, 3 gm. daily, was started after the biopsy. After four days of treatment the patient became afebrile and remained so. Complement fixation for Q fever was positive in a dilution of 1:512 on the twenty-second day of illness, and rose one week later to 1:1024.

*Case 3.* A 52 year old white male bartender was admitted to Highland-Alameda County Hospital on May 25, 1959, complaining of fatigue for one month and jaundice

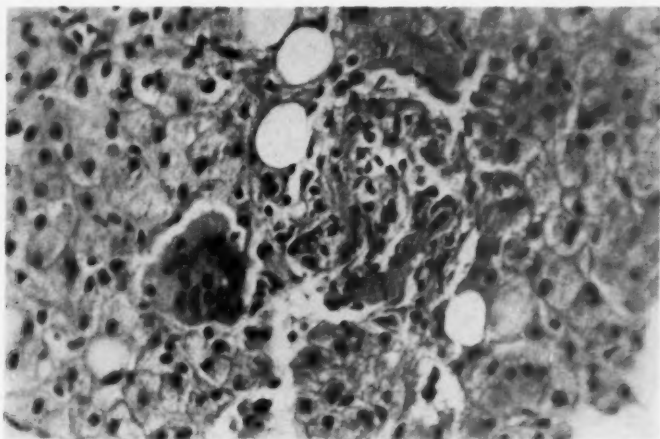


FIG. 4. *Case 2.* Liver biopsy. Increased magnification of a focus, showing a multinucleated giant cell and emphasizing the epithelioid character of the lesion. ( $\times 450$ .)

for five days. One month prior to admission he had had a four-day episode of chills, fever and myalgia. He attempted to return to work after his symptoms subsided, but for three weeks prior to admission profound fatigue forced him to bed. His urine had become dark five days prior to admission. He denied previous injections, exposure to jaundiced individuals, or fatty food intolerance. He admitted drinking one pint of whiskey daily for several years, but his dietary history seemed adequate. Five years previously he had had a subtotal gastrectomy because of bleeding peptic ulcer.

*Admission Physical Examination:* The temperature was 99.4° F.; pulse, 104. The patient was a well developed, well nourished white male who was mildly icteric. Examination of the heart and lungs was unremarkable. The liver extended 2 cm. below the right costal margin and 6 cm. above the right costal margin by percussion, and was soft, smooth and nontender. There was no palpable splenomegaly. A well healed midline surgical scar was present. The right testis was atrophic. The neurologic examination was within normal limits.

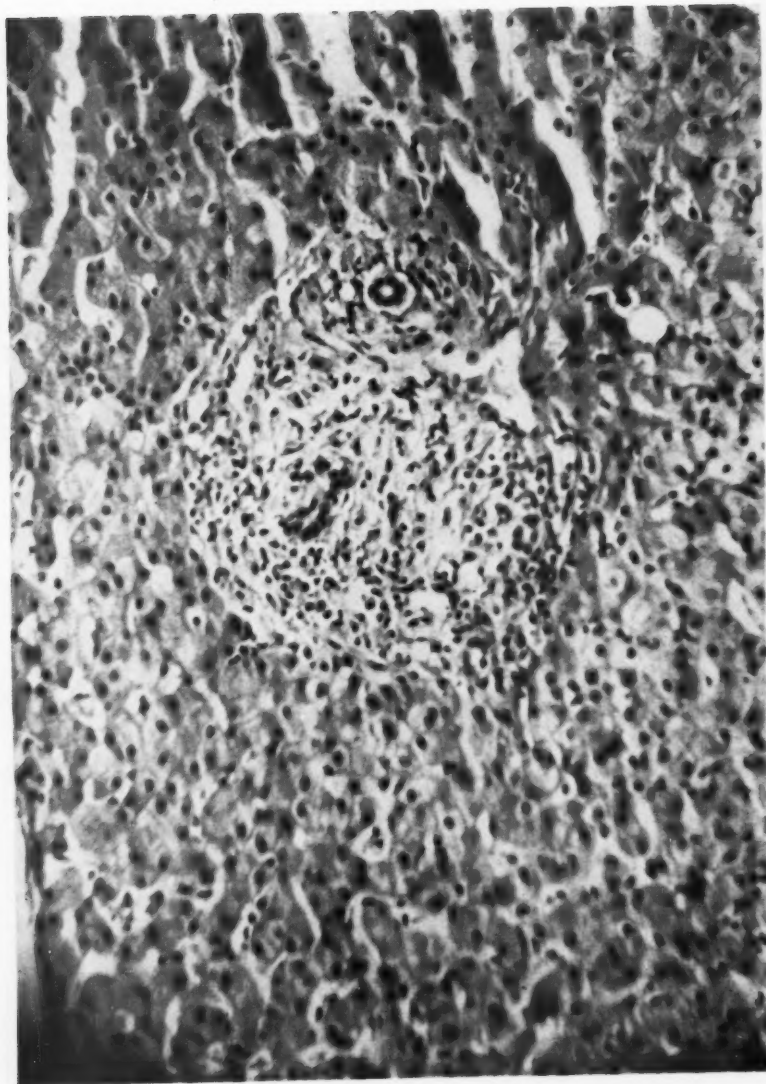


FIG. 5. Case 3. Liver biopsy, May 29, 1959, showing well preserved hepatic cells and an accumulation of acute and chronic inflammatory cells, necrotic liver cells, and fibrous tissue with a peripheral rim of histiocytes. A multinucleated cell is seen. (Photomicrograph, magnification  $\times 450$ .)

*Laboratory Work and Course:* Packed cell volume, 40%; white blood cell count, 7,800, with a normal differential; reticulocyte count, 3.2%; blood urea nitrogen, 14 mg.%. The urine showed 40 to 60 white blood cells per high power field, and a faint trace of albumin. Repeat urine examination showed 5 to 10 white cells per high power field, and a urobilinogen which was positive in a 1:10 dilution. Kolmer's test was 4 plus. (For the results of liver function tests see table 1.) Stools were negative for occult blood on two occasions. An L.E. cell preparation, a Paul-Bunnell heterophil agglutination, and agglutinations for typhoid and paratyphoid were normal.

The hematocrit fell to 28.5%, and there were associated tachycardia and drop in blood pressure following liver biopsy. Transfusion of 500 c.c. of whole blood stabilized the patient. Except for one white blood cell count of 13,200, the white cells remained normal in both total and differential count. Skin tests with histoplasmin, 1:100, coccidioidin, 1:100, and old tuberculin, 1:1000, were negative. Ten blood cultures and one bone marrow culture were negative. A urine culture grew out nonpigmented micrococci and gram-positive rods. Two sputum examinations were negative for acid-fast bacilli on smear. Guinea pig inoculation of the bone marrow and blood aspirated from the liver at the time of liver biopsy were negative. X-ray studies included chest films and excretory urograms, both of which were normal. An intravenous cholangiogram on June 2, 1959, failed to visualize. An electrocardiogram was normal.

The liver was biopsied twice, and both specimens showed scattered focal microscopic abscesses and granulomata (figure 5). On June 17, 1959, approximately the forty-seventh day of illness, the Q fever titer was 1:512.

For the first 10 hospital days the temperature spiked daily to 102° F. On the tenth day, chloramphenicol was started in amounts of 3 gm. a day. Two days later the patient was afebrile and remained so. He was discharged to be followed in the out-patient department, but failed to keep his appointment. (See table 1 for liver function studies.)

Although repeat complement fixation for Q fever, to demonstrate a changing titer, was not done in this case, the similarity to the other two proved cases, the high level of the titer and its occurrence during the epidemic seemed to warrant inclusion of the case in this report.

#### DISCUSSION

Granulomata in the liver, as in other organs, represent a nonspecific tissue reaction and are seldom diagnostic of any particular disease entity. Thus the clinician must usually rely on other clinical and laboratory evidence to diagnose correctly the process inciting the granulomatous response.

Popper<sup>8</sup> lists tuberculosis, sarcoidosis, berylliosis, histoplasmosis, brucellosis, schistosomiasis, syphilis and leprosy as disease states which may cause liver granulomata characterized by central necrosis surrounded by epithelioid and giant cells and demarcated by lymphocytes. He states that the situation is further confused by the occurrence of similar tubercles without any recognizable disease. The granulomata in the livers of our cases fulfilled the above described pathologic criteria. Q fever may thus be included in the differential diagnosis of liver granulomata.

It is notable that previous reports of Q fever with liver involvement have observed a generally less satisfactory response to the tetracycline drugs. We were interested to note a prompt and sustained beneficial effect from chloramphenicol in each of our cases, although all had marked liver disease.

## SUMMARY

Three cases of Q fever with predominant findings referable to the liver are presented. Each of these was found to have a granulomatous hepatitis on liver biopsy, and each had a prompt response to therapy with chloramphenicol.

## SUMMARIO IN INTERLINGUA

In tres patientes con un maladia a febrilitate acute, affection del hepate esseva constatate como un del major characteristics in le tableau clinic. Le anamnese non resolveva le question, sed biopsias hepatic demonstrava le presentia de hepatitis focal, distinguite per cellulas gigante, cellulas a inflammation chronic, e le formation de tissu epithelioide. Le characteristics histologic del specimens de biopsia hepatic esseva reguardate initialmente como congruente con tuberculosis, e le correcte diagnose esseva establite solmente post que le studio serologic habeva revelate un fixation de complemento congruente con febre de Queensland.

Ben que le occurrentia de hepatitis focal in casos de febre de Queensland ha essite reportate in le passato, le structura granulomatose del affection hepatic non esseva signalate.

Studios chimic revelava le presentia de un elevate livello de phosphatase alcalin e un reversion del proportion de albumina a globulina in omne le tres casos del presente reporto. In un del casos le indice de ictero esseva normal; in le altere duo, illo esseva levemente elevate.

Omne le tres patientes experienciava un prompte defervescentia e un progressive melioration clinic con 3 g de Chloramphenicol per die. Illes ha continuate trovar se ben depost lor dimission ab le hospital.

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## MYELOSCLEROSIS WITH SEROSAL MYELOID METAPLASIA AND FATAL LIVER INVOLVEMENT \*

By BORIS RUEBNER, M.D., *Baltimore, Maryland*

MYELOSCLEROSIS with a leuko-erythroblastic anemia and splenomegaly has become a well recognized clinical syndrome. Much controversy still surrounds its etiology, which may well be multiple.<sup>1</sup> The present case is thought worth reporting because of the unusual situation and marked fibrosis of some of the extramedullary foci, and also because of the severity of the hepatic involvement.

### CASE REPORT

*History:* A 67 year old night watchman of partly West Indian, partly European ancestry was first admitted to the Victoria General Hospital in 1951. He had been suffering from increasing weakness and fatigue during the preceding seven years.

On physical examination the patient was thin and had a rather dark complexion. He was lying in bed without undue distress. Vision was poor because of bilateral cataracts. Examination of ears, nose, throat, heart and lungs revealed no abnormal findings. The liver was felt four fingerbreadths below the costal margin, and the spleen extended halfway to the iliac crest. The remainder of the physical examination was negative. Blood pressure, 145/95 mm. Hg; pulse, 78 per minute; temperature, 99° F. Urinalysis was normal. The fasting blood sugar concentration was 78 gm.%; nonprotein nitrogen, 27 mg.%. Plasma protein level, 7.3 gm.%; alkaline phosphatase, 6.8 units (Shinowara). The bromsulfalein test showed 5.5% retention after 30 minutes. Kahn test was negative. The initial hemoglobin was 9.6 gm.%. There was anisocytosis. The red cells were normochromic and tended to be microcytic. The white blood count was 4,200 per cubic millimeter, with 1% myelocytes, 4% metamyelocytes, 72% polymorphonuclear leukocytes, 19% lymphocytes and 4% monocytes. Sternal marrow aspiration was unsuccessful. Roentgenograms revealed several small areas of decreased bone density in the upper thirds of both humeri, particularly the left. A presumptive diagnosis of myelosclerosis with extramedullary (splenic) hemopoiesis was made. After blood transfusion, the patient was discharged to continue under out-patient care.

During the following years, in spite of gradually losing some 12 pounds in weight, the patient continued to feel reasonably well and was able to remain at work. He required periodic blood transfusions and, because of abdominal discomfort, was given irradiation to the spleen (200 r) in 1955. At that time his plasma protein concentration was 6.7 gm.%. Subsequently one of his cataracts was enucleated, and in 1956 roentgen therapy to the spleen was repeated (300 r).

In March, 1957, the patient was re-admitted to the Victoria General Hospital because of severe diarrhea and some abdominal pain and swelling which had lasted for 10 days. On physical examination he was markedly emaciated. Gross ascites was present. After paracentesis a large, firm, irregular spleen was palpable. The liver was no longer palpable. Blood pressure, 82/62 mm. Hg; pulse, 100 per minute; temperature, 100.6° F. Laboratory studies showed a serum protein level of 5.7 gm.%, (albumin, 3.4 gm.%;); alkaline phosphatase, 7.9 units; bilirubin, 0.52 mg.%.

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The plasma sodium was 133.4 mEq./L.; chloride, 104.8 mEq./L.; potassium, 4.1 mEq./L. The bromsulfalein test showed 14% retention after 30 minutes. Hemoglobin, 8 gm.%; white cell count, 4,250 per cubic millimeter, with 5% myelocytes, 3% metamyelocytes, 46% polymorphonuclear leukocytes, 44% lymphocytes and 2% nucleated red cells. Platelets were plentiful. Bacteriologic examination of the feces for *Salmonellae*, *Shigellae* and *Staphylococcus pyogenes* was negative. Roentgenograms showed a hiatal hernia and suggested the presence of esophageal varices. Mottled osteosclerosis affecting the dorsal spine and thoracic cage was present. During the patient's stay in hospital two abdominal paracenteses of approximately 4,000 c.c. each were performed. Clear fluid of a specific gravity of 1.011 was obtained. The diarrhea improved with tetracycline therapy. Because of the sudden development of ascites, portal vein thrombosis was suspected. After discharge the patient's condition remained fair, in spite of bouts of diarrhea and some abdominal distention.

On October 27, 1957, the patient had to be re-admitted because of hematemesis. On physical examination he was pale, restless and uncoöperative. The abdomen was protuberant, and there were marked splenomegaly, ascites and prominent superficial veins. Small lymph nodes were palpable in his axillae and groins. Blood pressure, 110/65 mm. Hg; pulse, 90 per minute; temperature, 98° F. Laboratory investigations showed a serum protein concentration of 4.9 gm.% (albumin, 2.8 gm.%); bilirubin, 0.8 mg.%; nonprotein nitrogen, 43 mg.%; thymol turbidity, 4.7 units. The prothrombin time was normal. Plasma sodium was now 123.3 mEq./L.; chlorides, 109.5 mEq./L.; potassium, 5.1 mEq./L. The hemoglobin was 4.9 mg.%. The white and differential blood counts were essentially unchanged. The feces were positive for occult blood. In spite of repeated blood transfusions, the patient's condition did not improve greatly, and he died on November 15, 1957, after another severe hematemesis.

*At necropsy*, the subject was an extremely emaciated elderly male with a dusky complexion. There was marked abdominal distention but no generalized edema.

The abdominal cavity contained about 5,000 c.c. of clear, straw-colored fluid. Firm, white nodular deposits were present in the right ileocecal region and in front of the sacrum. The largest deposit weighed 30 gm. and, on section, was of a uniform white.

The liver was light brown and normal in shape and size (1,520 gm.). Its surface was finely nodulated in most areas. The nodules were approximately 0.5 cm. in diameter. On section, the entire liver had a moderately severe nutmeg appearance. The nodularity of the liver affected an outer rim approximately 1 cm. thick. The capsule was generally slightly thickened, to approximately 0.1 to 0.2 cm. The capsular thickening was increased near the origin of the falciform ligament on the diaphragmatic surface. In this situation there was a white plaque, 4 cm. in diameter and 0.7 cm. in thickness, and similar to the plaques in the presacral and ileocecal areas described above (figure 1). The intrahepatic portions of the left and right main branches of the portal vein from the porta hepatis almost to the capsular surface of the liver were surrounded by a cuff of white fibrous tissue 0.2 to 0.3 cm. thick. The hepatic parenchyma adjacent to these major intrahepatic branches of the portal vein was nodular and showed an increase in the periportal fibrous tissue (figure 2).

The gall-bladder was normal and the biliary tract was patent. The bile duct, however, was surrounded by a cylindric white mass, 1 cm. in diameter, which was similar to the other plaques already described in the abdominal cavity. The portal vein was not thrombosed, and its intrahepatic branches were also patent.

The spleen was firm and enlarged, weighing 1,700 gm. Its surface was grayish blue. The cut surface was dark brown and had a uniform, fleshy appearance. The





FIG. 1. Section of the plaque on the capsular surface of the liver near the origin of the falciform ligament. Underlying this plaque there is well marked nodularity of the liver. Hematoxylin and eosin  $\times 6$ .



FIG. 2. Section of the liver, including one of the main intrahepatic branches of portal vein, which is surrounded by a cuff of fibrous tissue. The adjacent hepatic parenchyma is nodular. Hematoxylin and eosin  $\times 12$ .

splenic vein was patent and markedly dilated. The lower end of the esophagus was bluish and showed many dilated veins below the mucosa. No actual ulceration could be found.

The stomach and the entire intestine to the rectum were distended with dark red fluid blood and blood clot. No ulceration was present in the gastrointestinal tract. The lumen of the appendix was replaced by white fibrous tissue. The other abdominal organs, including the genitourinary tract, were not remarkable. There was no thrombosis of the mesenteric vessels.

The heart weighed 280 gm. and was normal except for some coronary atheroma. The lungs showed no consolidation, but there were several white nodules on the visceral pleura up to 0.5 cm. in diameter which were similar to the larger nodules present on the serosa.

The vertebral marrow was uniformly pinkish gray on section, and did not have the normal marrow architecture.

Microscopic sections of bone marrow from the lumbar vertebrae showed the marrow spaces to be occupied by fibrovascular connective tissue which varied considerably in cellularity in different areas. In some areas there was marked proliferation of myeloid cells and giant cells, with evidence of new bone formation and osteoclastic resorption (figure 3). In others, the marrow was replaced by poorly cellular fibrous tissue, and the bony lamellae showed little remodeling (figure 4).

The splenic capsule and trabeculae were somewhat thickened. The pulp was diffusely infiltrated by myeloid cells, including many megakaryocytes, and showed a mild, diffuse fibrosis (figure 5). Many of the vessels contained islands of hemopoietic cells similar to those in the parenchyma, but neither in the spleen nor in any of the other organs were there any actual thrombi. Only a few small malpighian corpuscles could be seen.

The entire liver capsule was slightly thickened by fibrous tissue containing scattered small groups of hemopoietic cells. The periportal fibrous tissue of the lobules subjacent to the capsule showed fibrosis, and there was distortion of the hepatic architecture, with evidence of regeneration (figure 1). Many of the liver lobules adjacent to the intrahepatic branches of the main left and right portal veins showed fibrosis and distortion similar to that seen in the subcapsular zone (figure 2). Moderate numbers of chronic inflammatory cells were seen in the fibrosed portal triads of the distorted lobules. Many acini which were more than 1.0 cm. from the liver surface and some distance from the major intrahepatic portal veins showed no fibrosis or distortion. Foci of myeloid cells, including many giant cells, were scattered throughout the hepatic parenchyma. There was a tendency for these foci to be situated in the centrilobular areas (figure 6). Many branches of the portal and hepatic veins were partially filled with groups of myeloid cells like those seen in the splenic vessels. The liver cells generally showed little abnormality, but some atrophy was present in the center of the lobules near foci of hematopoiesis. A few small areas of hydropic degeneration were scattered irregularly throughout the liver. Hemosiderin pigment was present in a few Küpffer's cells only. No fatty change was evident. The white plaque on the diaphragmatic surface of the liver consisted of fibrovascular tissue which, in some parts, was quite densely collagenized. Foci of myeloid cells with large prominent periodic acid Schiff positive giant cells were scattered throughout it (figure 7). The distortion of the hepatic architecture was most marked in the lobules underlying this plaque.

The bile duct was surrounded by tissue resembling that of the white plaque on the liver surface. The deposits on the serosal and parietal peritoneal surfaces and in the appendix consisted of similar tissue.

A lymph node from the porta hepatis was markedly fibrosed and contained a

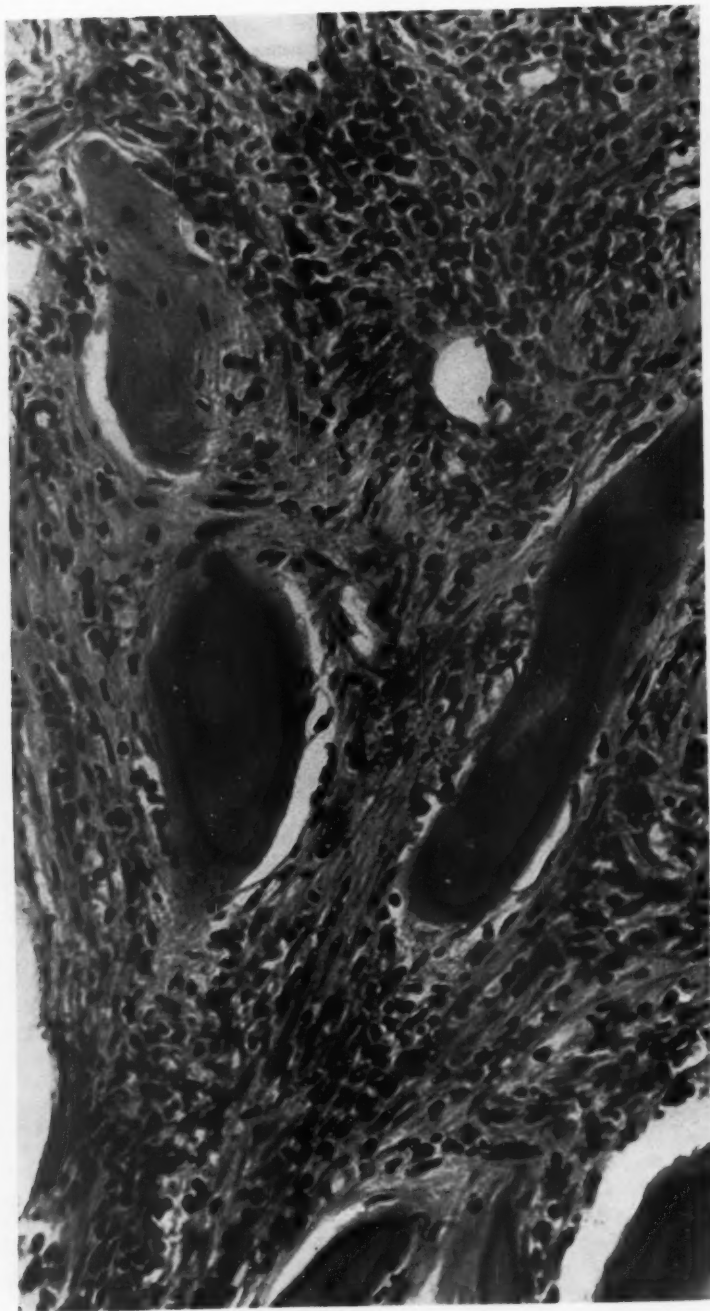


FIG. 3. Section of bone marrow from lumbar vertebra, showing marked proliferation of myeloid cells, including some giant cells. New bone formation and osteoclastic resorption have taken place. Hematoxylin and eosin  $\times 230$ .

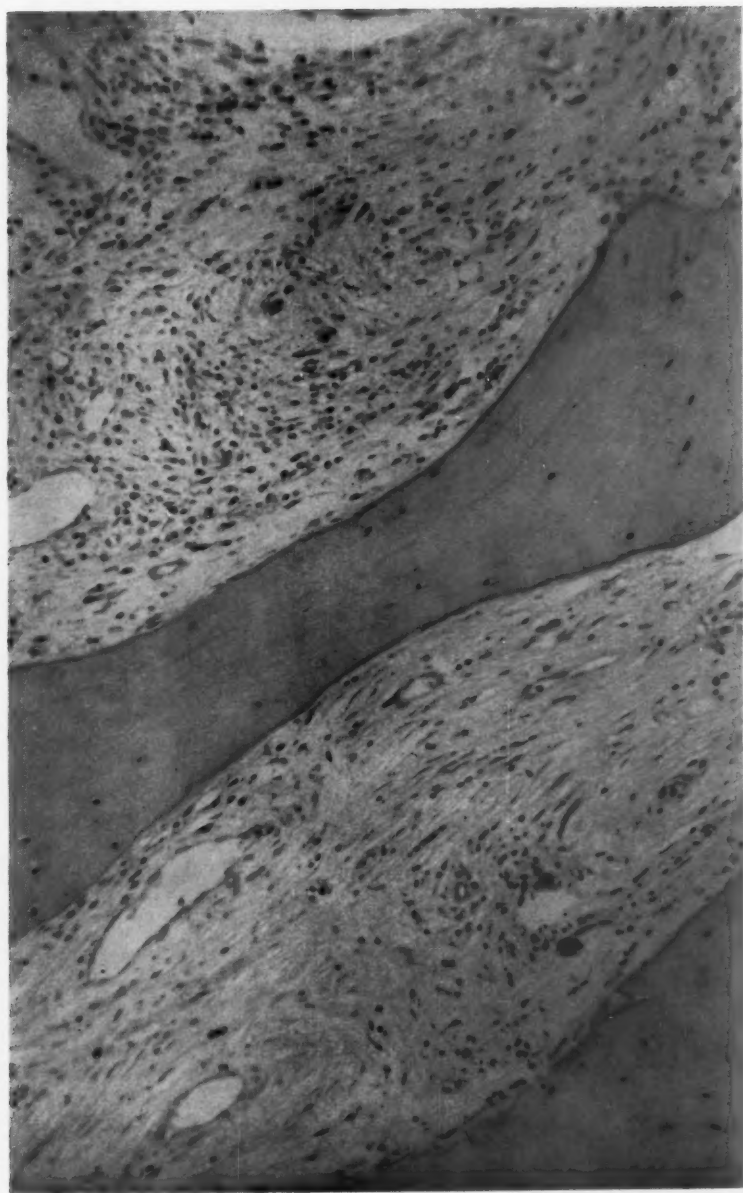


FIG. 4. Another section of bone marrow from a lumbar vertebra. The marrow is replaced by poorly cellular fibrous tissue, and the bony lamellae show little remodeling. Hematoxylin and eosin  $\times 90$ .

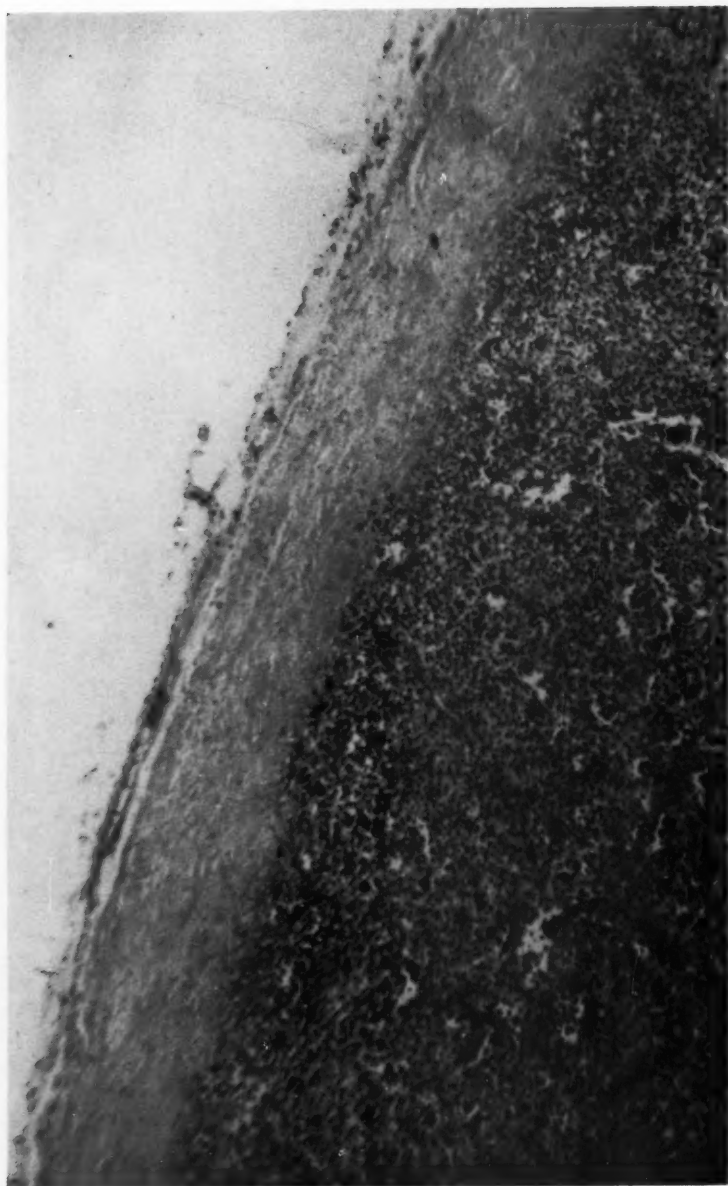


FIG. 5. Section of spleen. There is some thickening of the capsule. The pulp is diffusely infiltrated by myeloid cells, including many megakaryocytes. There is little fibrosis. Hematoxylin and eosin  $\times 90$ .



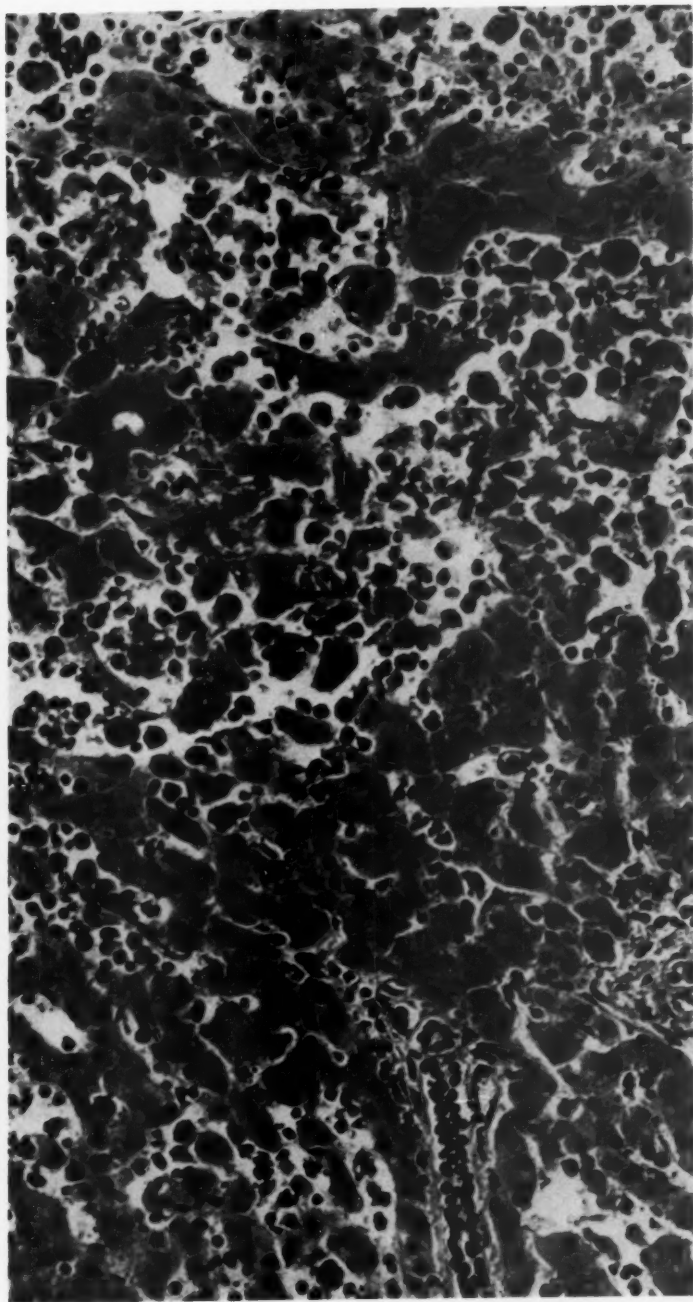


FIG. 6. Section of liver showing focus of myeloid cells in the parenchyma. These foci tend to be situated in the centrilobular area. Hematoxylin and eosin  $\times 230$ .



Fig. 7. High power view of the plaque on the surface of the liver shown in figure 1. The plaque consists of fibrovascular tissue which is densely collagenized in some parts. Foci of myeloid cells with prominent periodic acid Schiff positive giant cells are scattered throughout it. Hematoxylin and eosin  $\times 230$ .

few foci of myeloid cells. Many other lymph nodes, including some situated quite close to foci of myeloid cells, appeared to be normal.

The kidneys showed mild arteriosclerotic changes. A small focus of myeloid cells without fibrosis was present in the medulla near the pelvis.

In the wall of the esophagus there were many greatly dilated veins, some of which contained groups of myeloid cells.

#### COMMENT

The bone marrow showed myelosclerosis of advanced fibrous type. The usual extramedullary hemopoiesis was present in the spleen, and to a much lesser extent in the kidney. The fibrous tissue surrounding the intrahepatic course of the principal portal veins and the nodule on the surface of the liver had essentially the same morphology as the marrow. So did a lymph node from the porta hepatis, the tissue surrounding the bile duct and the deposits in the appendix, retroperitoneal fat and pleura. The positive Schiff's reaction given by the cytoplasm of the giant cells in these areas confirmed the morphologic impression that these cells were megakaryocytes and not Dorothy Reed cells.<sup>2</sup> The deposits of extramedullary hemopoiesis were unusual both in their situation and in the marked sclerosis which they had undergone. Extramedullary hemopoiesis may occur in the lymph nodes, retroperitoneal fat and pleura<sup>3</sup> but there appears to be no previous record of such deposits surrounding the bile ducts or situated in the lumen of the appendix. The formation of tumor-like mesenteric deposits is very rare in myelosclerosis. Only three cases have been reported previously.<sup>4</sup> It is possible that these nodules represent foci of extramedullary hemopoiesis which have subsequently undergone the same fate as the marrow. The alternative view, which appears rather more likely, is that the whole disease is one of the neoplastic myeloproliferative disorders discussed by Dameshek.<sup>5</sup> The serosal deposits in this patient could represent multicentric myeloid metaplasia, or could be due to metastasis. The latter view is supported by the finding of myeloid cells in the veins of the liver, spleen and esophagus. The present case therefore adds some further evidence in favor of the neoplastic etiology of at least some cases of myelosclerosis, and supports the suggestion of Vaughan and Harrison<sup>6</sup> that marrow sclerosis and leuko-erythroblastic hyperplasia occur simultaneously in response to some unidentified stimulus.

Involvement of the liver by extramedullary hemopoiesis has been recognized in myelosclerosis for a long time, but in the present case the severity of the hepatic involvement was striking both during life and at autopsy. When first seen, the patient had marked hepatic enlargement. This could no longer be detected six years later, and at autopsy the liver was found to be of normal size. There was capsular and intrahepatic fibrosis, however, which may well have been responsible for some shrinkage of the liver. Progressive impairment of hepatic function was also suggested by a gradual fall in the plasma albumin and the development of bromsulfalein retention. Ascites developed eight months before the patient's death due to hemorrhage from ruptured esophageal varices.

Cirrhosis of the liver and portal hypertension have occasionally been referred to in published reports of myelosclerosis. Wyatt and Sommers<sup>1</sup> noted an association of hematemesis and cirrhosis with myelosclerosis in two of their patients. Leonard, Israels and Wilkinson<sup>7</sup> also found this combination in two

cases. Linman and Bethell<sup>8</sup> observed that two of their patients were suffering from ascites. In the present case, fibrosis and regeneration nodules could be seen both on the surface of the liver and in the hepatic parenchyma surrounding the principal intrahepatic branches of the portal vein. This change was particularly marked in that part of the liver which was underlying the large serosal nodule of myeloid proliferation. The hepatic fibrosis in this area at least, and probably also elsewhere in the liver, seemed to be a response to the myeloid proliferation. It is probable that the cirrhotic process in this patient was the principal factor responsible for the portal hypertension which led to death caused by hemorrhage from esophageal varices. Excessive splanchnic blood flow due to splenomegaly (1,700 gm.) was almost certainly present, and may well have contributed to the portal hypertension.<sup>8</sup>

Ascites in liver disease is usually due to the combined action of several factors, the relative importance of which varies in different cases.<sup>10</sup> Both in experimental animals and in patients with liver disease, portal hypertension is only one of these factors. Progressive constriction of the portal vein does not produce ascites in dogs,<sup>11</sup> and in patients suffering from portal vein thrombosis, ascites occurs only if the plasma protein concentration is reduced.<sup>12</sup> In our patient the plasma protein level was normal when he was first seen. During his last year of life, there was marked hypoalbuminemia (2.8 gm.%), which undoubtedly contributed to his ascites, and also represented clinical evidence of liver cell damage. Histologically, there was relatively mild centrilobular atrophy in relation to foci of extramedullary hemopoiesis. Scattered areas of hydropic degeneration were also present, but there was no fatty change. An increased blood level of antidiuretic substances (V.D.M., aldosterone) occurs commonly in patients with liver disease.<sup>10</sup> Although these substances were not estimated, it is probable that they contributed to his ascites. His serum sodium level was extremely low during his terminal illness (123 mEq./L.). Such levels indicate severe liver failure and a very poor prognosis.<sup>13</sup>

It is suggested that the liver damage and portal hypertension in this case were the result of an unusual cirrhotic process similar to the sclerosis of the bone marrow. The normal globulin level and thymol turbidity are further evidence that this was not an ordinary cirrhosis of the liver. It is concluded that, in some patients with myelosclerosis, cirrhosis of the liver and portal hypertension may not be incidental findings but may be due to a lesion analogous to that occurring in the bone marrow.

#### SUMMARY

This report describes the clinical course and postmortem findings in an elderly male with myelosclerosis. After many years during which anemia was responsible for his chief complaints, he developed ascites with liver failure. He finally died from hematemesis.

At necropsy there was myelosclerosis of advanced fibrous type. The usual extramedullary hemopoiesis was present in the spleen. Fibrous nodules of a morphology similar to that of the marrow were present on the visceral pleura, in the right ileocecal region, in front of the sacrum, and on the surface of the liver. Similar material was found in the appendix and surrounding the common bile duct. These areas of myeloid metaplasia were unusual both in the marked sclerosis which they had undergone and in their situation on serosal sur-

faces. It is considered that this case adds evidence in favor of the neoplastic etiology of at least some cases of myelosclerosis.

Hepatic involvement was striking both during life and at autopsy. Fibrosis of patchy distribution with regeneration nodules was found through the liver. This change was most marked near the capsular deposit of extramedullary hemopoiesis and adjacent to the intrahepatic course of the principal portal veins. It is suggested that these changes were responsible for the portal hypertension and other signs of liver failure, and it is concluded that in some patients with myelosclerosis there may be a hepatic lesion analogous to that of the bone marrow and causing an unusual type of cirrhosis.

#### ACKNOWLEDGMENTS

I wish to thank Professor C. V. Harrison for his kindness in giving his opinion on the sections, and Mr. C. S. Brindle for taking the photographs.

#### SUMMARY IN INTERLINGUA

Es describe le curso clinic e le constataiones necroptice in un caso de myelosclerosis in un masculo de etate avanzate. Post multe annos durante le quales anemia habeva essite su gravamine principal, ille disveloppava ascites con disfallimento hepatic e moriva finalmente de hematemesis.

Le necropsia revelava myelosclerosis del typo fibrose avanzate. Le usual hematopoiese extramedullari esseva presente in le splen. Nodulos fibrose de un morphologia simile a illo del medulla esseva presente in le region dextero-ileocecalle, ante le sacro, e al superficie del hepate. Un simile material esseva trovate in le appendice e circum le ducto biliari commun. Iste areas de metaplasia myeloide esseva inusual tanto per le marcate sclerose que illos habeva disveloppate como etiam per lor sites. Es opinata que iste caso reinfortia le conception que al minus certes del casos de myelosclerosis ha un etiologia neoplastic.

Le affection del hepate esseva frappante, durante le vita del patiente e etiam in le necropsia. Fibrosis con nodulos de regeneration esseva distribuite in maculas irregular in omne partes del hepate. Iste alteration esseva le plus marcate proxime al deposito capsular de hematopoiese extramedullar e adjacente al curso intrahepatic del principal venas portal. Es opinata que iste alterationes esseva responsabile pro le hypertension portal e le altere signos de disfallimento hepatic. Le conclusion es que il existe in certe patientes con myelosclerosis un lesion hepatic que es analoge al lesion del medulla ossee e que causa un typo inusual de cirrhosis.

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## EDITORIALS

### A NEW EDITOR

THE ANNALS OF INTERNAL MEDICINE has a new Editor. This fact presents the readers, the writers, and the Editor with a very real measure of uncertainty. The reader is uncertain of the future character of the journal, of the type of material that will be presented to him, of its usefulness to him as a physician. The contributor is uncertain not only of the suitability of his paper to the journal but of the reverse, as well. The new Editor is the most uncertain of all for his is the problem that faces each new generation in every process of life. This is the dual problem of fulfilling the past and of meeting the future, of maintaining advances and standards already achieved and of responding to the challenges that lie ahead. To allay all these uncertainties what prognosis can we give in this neo-natal time for the infant ANNALS of the new generation? What can we tell of its purpose and course?

The purpose of the ANNALS OF INTERNAL MEDICINE is unchanged and may be stated quite simply: it is to help the practicing physician, particularly the physician specializing in internal medicine, to be a better physician. The accomplishment of this purpose is less simple and constitutes the challenge facing the new Editor in the present-day setting of tremendously rapid advances in pure and applied biological science.

In the world of medicine today no valid division remains between experimental or laboratory medicine and clinical medicine. The explosive acquisition of new knowledge in such fields as physiology, biochemistry, genetics, and metabolism compels the physician not only to strive to be a better physician but indeed to become a human biologist if he is to continue to provide the best available care for his patients. And in an age when political action, through nuclear and biological warfare, threatens to negate *in toto* the age-long efforts of the healing professions, the physician, especially, must endeavor also to be an intelligent and informed citizen. Beset thus with the explosion of scientific knowledge on one hand and the explosions of population and nuclear warfare on the other, the physician-biologist-citizen bears a particularly great obligation to his fellowmen. And yet the physician is but human; his time is short and the demands on him are long. Amidst the pressures of busy practice and community life he needs every assistance that he can get to keep his professional and scientific education moving forward. Can the ANNALS help him in his dilemma? We believe that it can.

The new Editor and his associates approach this task with humility. We have to learn how to edit a journal and, more to the point, we have to

learn how to do it to attain the objectives stated above. We have the whole-hearted backing of the Committee on Publications and the Regents of the College. We are drawing together an editorial board of national scope to which we shall turn for advice and assistance. Certain specific features for the *ANNALS* are planned. We hope to attract good reports of original work in the fields of basic science and clinical investigation, work which has particular implications for clinical medicine. We intend to continue the reporting of clinical material. In addition it is hoped to publish an increased number of broad but succinct reviews of subjects that will help the busy physician to keep abreast of the rapid progress of medical and biological science. These are the first order of business. Of second order are such factors as format, typography, size, general attractiveness and readability. Consideration of these factors will be undertaken but not in haste, for we believe in evolution, not revolution, of the *ANNALS*. To this end we solicit both the patience and the opinions of our readers.

The *ANNALS* is a medium of communication. The essence of good communication is clarity of the thought to be conveyed and clarity of the form in which that thought is transmitted. Hence we dedicate ourselves to good ideas, high scientific standards, sound grammar, clear style. The extent to which we succeed will depend not only on the coöperation of our contributors and readers but on our ability to educate ourselves. We will try.

J. R. E.

#### *PENICILLAMINE: THE PHARMACOLOGY OF A CHELATING AGENT\**

SOME four years ago the aminoacid dimethylcysteine (penicillamine) was introduced into clinical medicine as a chelating agent<sup>1,2</sup> and the time is now ripe to review what is known of the chemistry, pharmacology and therapeutic action of this compound.

It was a result of urgent war time research into the chemistry of the penicillins that led to the discovery of a new aminoacid which received its name, penicillamine, from the parent compound.<sup>3</sup> Some years later it was shown to be a sulphur aminoacid structurally related to cysteine, but differing from it by the addition of two methyl groups to the  $\beta$  carbon atom.<sup>4</sup>

Penicillamine can be prepared synthetically by the introduction of sulphur into the valine molecule thus:

\* From the Department of Experimental Medicine, University of Cambridge, England.

<sup>1</sup> Walshe, J. M.: Wilson's disease, a new oral therapy, *Lancet* 1: 25, 1956.

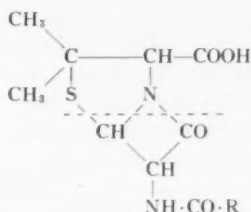
<sup>2</sup> Walshe, J. M.: Penicillamine, a new oral therapy for Wilson's disease, *Am. J. Med.* 21: 487, 1956.

<sup>3</sup> Abraham, E. P., Chain, E., Baker, W., and Robinson, R.: Penicillamine, a characteristic degradation product of penicillin, *Nature (Lond.)* 151: 107, 1943.

<sup>4</sup> Chain, E.: Components of the penicillin molecule, in *Antibiotics*: Vol. 2. Chapter 22, Oxford University Press, 1949.



By this method either the D, the L or the DL isomers can be prepared, depending on the optical activity of the parent compound. A simpler preparation is by the acid hydrolysis of penicillin, in which case the D enantiomorph is obtained, a considerable therapeutic advantage as will be shown later. Although penicillamine composes approximately 40% of the penicillin molecule the yields obtained in practice seldom achieve more than half of this quantity. The position of penicillamine in the penicillin molecule is shown in the accompanying structural formula:



The terminal group, R, varies with the penicillin, F, G, K or X. On analysis dimethyl cysteine proved to be more stable to oxidation than cysteine and neither the D nor the L isomers appeared to be oxidized by enzymes occurring in the animal body.<sup>4</sup>

The biological importance of penicillamine was first studied in du Vigneaud's laboratory.<sup>5,6</sup> L-penicillamine was shown to be a powerful growth inhibitor in young albino rats and its continued administration led, in a relatively short time, to convulsions and death. Curiously enough the addition of cystine, cysteine, homocystine or homocysteine to the diet gave no protection, but ethanolamine, its N-methyl derivatives or choline, all completely reversed these toxic effects. D-penicillamine, on the other hand, appeared to be without biological activity. Later work from the same department<sup>7,8</sup> has done much to account for the growth inhibitory properties of L-penicillamine. Kuchinskas and du Vigneaud<sup>7</sup> observed a striking similarity between penicillamine-treated animals and those on a pyridoxine (vitamin B<sub>6</sub>) deficient diet. They were able to show that pyridoxine gave complete protection against the toxic action of L-penicillamine. *In vitro*

<sup>5</sup> Wilson, J. E., and du Vigneaud, V.: L-Penicillamine as a metabolic antagonist, *Science* **107**: 653, 1948.

<sup>6</sup> Wilson, J. E., and du Vigneaud, V.: Inhibition of the growth of the rat by L-penicillamine and its prevention by aminoethanol and related compounds, *J. Biol. Chem.* **184**: 63, 1950.

<sup>7</sup> Kuchinskas, E. J., and du Vigneaud, V.: An increased vitamin B<sub>6</sub> requirement in the rat on a diet containing L-penicillamine, *Arch. Biochem. and Biophys.* **66**: 1, 1957.

<sup>8</sup> du Vigneaud, V., Kuchinskas, E. J., and Horvath, A.: L-penicillamine and rat liver transaminase activity, *Arch. Biochem. and Biophys.* **69**: 130, 1957.

penicillamine rapidly forms a thiazolidine with pyridoxal-5-phosphate,<sup>7,8</sup> this probably also occurs *in vivo* and accounts for the inhibition of such pyridoxal dependent enzymes as the transaminases and kynureninase, and this in turn would account for the abnormal tryptophan metabolism observed in L-penicillamine treated rats. The ability of choline or ethanolamine to protect against penicillamine toxicity, however, remains obscure.

While the toxicity of L-penicillamine has been well established and its action as a pyridoxine antimetabolite elucidated, less work has been done on the non-toxic D isomer. However there is evidence to suggest that the latter compound has growth promoting properties for the chick and pig.<sup>9</sup> A synergistic action has also been demonstrated between penicillamine and various other antibiotics, although D-penicillamine itself has no antimicrobial activity.<sup>10</sup>

A more detailed study of the action of the penicillamines on bacterial metabolism has been carried out by Aposhian and his associates.<sup>11, 12, 13</sup> They showed that some isomers of penicillamine inhibit metabolism of the ethanolamine precursor serine by *Leuconostoc mesenteroides* P-60, an interesting observation in view of the ability of ethanolamine to protect against the toxic action of L-penicillamine on rats. In another species of organism, *Escherichia coli*, only L-penicillamine had a growth inhibitory action and this was reversed by the addition to the media of leucine, isoleucine, valine or methionine, whereas glutathione, serine and 18 other aminoacids gave no protection, neither did pyridoxine, choline or ethanolamine. *In vitro* studies<sup>13</sup> also yielded useful information; the earlier report by Chain,<sup>4</sup> that L-penicillamine was not oxidized by L-aminoacid oxidase was confirmed, but the D-aminoacid was shown to be slowly attacked by D-aminoacid oxidase. Neither isomer was active as a substrate for L-cysteine desulphurase. In the light of these studies Aposhian<sup>13</sup> suggested that L-penicillamine is inactivated *in vivo* by combination with pyridoxal to form a thiazolidine, whereas D-penicillamine is slowly attacked by D-aminoacid oxidase.

The introduction of penicillamine into clinical medicine may be said to date back to the chance finding of an unknown aminoacid in the urine of a patient with liver disease. This was isolated and identified as  $\beta, \beta$  dimethylcysteine.<sup>14</sup> During the course of this isolation it became apparent that,

<sup>9</sup> Taylor, J. H., and Gordon, W. S.: Growth promoting activity for pigs of inactivated penicillin, *Nature* (Lond.) **176**: 312, 1955.

<sup>10</sup> Scherr, G. H., and Bechtle, R. M.: Studies on synergists for antimicrobial agents. *Antibiotics Annual* 1958-59, p. 855, Medical Encyclopedia, New York, N. Y.

<sup>11</sup> Aposhian, H. V., Wolff, S. M., and Rhea, W. G.: The inhibition of serine metabolism in *Leuconostoc mesenteroides* P-60. I. Microbiological activity of D- and L-penicillamine, *Arch. Biochem. and Biophys.* **71**: 442, 1957.

<sup>12</sup> Blair, R. M., and Aposhian, H. V.: The inhibition of *Escherichia coli* by L-penicillamine and its reversal by isoleucine, valine or leucine, *Biochim. biophys. acta* **30**: 214, 1958.

<sup>13</sup> Aposhian, H. V., and Bradham, L. S.: Metabolism *in vitro* of the sulphhydryl aminoacids L- and D-penicillamine, *Biochem. pharmacol.* **3**: 38, 1959.

<sup>14</sup> Walshe, J. M.: Disturbances of aminoacid metabolism following liver injury, *Quart. J. Med.* **22**: 483, 1953.

unlike cysteine, the dimethyl analogue remained in the reduced or  $-SH$  form in the body and was excreted as such in the urine. The source of the penicillamine was parenterally administered penicillin which presumably underwent degradation in the body. This finding was in keeping with an earlier one that breakdown products of penicillin, containing labelled sulphur, appeared in the urine within a few hours of the parenteral administration of the antibiotic to normal animals.<sup>15</sup>

These observations on the excretion of penicillamine in human urine,<sup>14</sup> which originally appeared to be of theoretical interest only, were later put to good account by the trial of penicillamine as a chelating agent in the treatment of Wilson's disease.<sup>1,2</sup> Penicillamine had been shown to possess a stable  $-SH$  group, which was not oxidized in the body, which should therefore be available, as a mercaptan, for complexing or chelating divalent metals. An analogy might be drawn here with the use of BAL (dimercapto-propanol) in the treatment of arsenical poisoning. This compound was originally designed by Peters, Stocken and Thompson<sup>16</sup> as an antidote to Lewisite poisoning during the war, the 2  $-SH$  groups being needed to form a stable ring with monosubstituted trivalent arsenic. Glutathione and other monothiols were, however, found to be equally satisfactory in the management of disubstituted arsenical toxicity. The monothiol, penicillamine, should therefore be active against divalent metals and, if derived from penicillin, should be the non-toxic, metabolically inert D aminoacid. Initially the greatest difficulty to be overcome before clinical trials could be carried out was in obtaining supplies of the aminoacid. Once this was available it became apparent that penicillin was a powerful chelating agent able to mobilize copper not only from patients with Wilson's disease but also from normal subjects.<sup>1</sup> A later and more detailed study showed that penicillamine was very much more active than BAL as a cupruritic in five out of six cases of Wilson's disease studied and it was suggested that this compound deserved clinical trial in other heavy metal intoxications.<sup>2</sup> Two big advantages it offered over previously available chelating agents were its activity when given by mouth and the apparent lack of toxic side effects of the D isomer, although it has given rise to occasional sensitivity reactions in persons also sensitive to penicillin. A number of other sulphur compounds tested at the same time, cysteine, methionine, cysteamine, thiourea and diethyl dithiol terephthalic acid were all inactive as cupruritics. At the same time it was pointed out that the exact nature of the penicillamine copper linkage was unknown, the copper atom might be held as a bridge between the  $-SH$  radicals of two penicillamine molecules or bound in a ring between  $-SH$  and either  $-NH_2$  or  $-COOH$  group of the aminoacid. Speculation on the mode of action of penicillamine led to the sug-

<sup>15</sup> Rowlands, S., Rowley, D., and Stewart, H. C.: Absorption and excretion studies with radioactive penicillin, *Lancet* **2**: 493, 1948.

<sup>16</sup> Peters, R. A., Stocken, L. A., and Thompson, R. H. S.: British antilewisite: BAL, *Nature* (Lond.) **156**: 616, 1945.

gestion that it removed copper from a sulphhydryl dependent enzyme system, possibly necessary for the proper functioning of the Krebs cycle.<sup>2</sup>

A chelating agent given by mouth might bind more of the metal under study in the gut than it eventually removed from the body so that, despite an apparently good yield in the urine the net result would be a positive balance. That this was not the case with penicillamine was shown both by giving the compound intravenously and also by estimating its ability to mobilize previously injected radioactive copper.<sup>17</sup>

Following up the theory that penicillamine might act by removing copper from an —SH dependent enzyme system Hill and Walshe<sup>18</sup> suggested that one such vulnerable enzyme was reduced coenzyme A. They therefore investigated pyruvate metabolism in three patients with Wilson's disease and found that in two, who had received little or no previous therapy, this was disturbed, while in a third patient, who had been treated first with BAL and then with penicillamine for several years, there was no abnormality. The two patients with disordered pyruvate metabolism were then treated with short courses of penicillamine, this was followed by a return towards normality of the elevated blood pyruvate levels. These preliminary results have been extended and in a series of 16 patients 10 showed abnormal pyruvate metabolism which was apparently corrected by penicillamine in six.<sup>19</sup> Other studies on the mechanism of penicillamine action have demonstrated its ability to free copper from caeruloplasmin and other protein linkages and thereby to render it available for excretion at the glomerulus. This observation has been supported by *in vitro* studies in which incubation of plasma or pure caeruloplasmin with penicillamine has resulted in the protein bound copper being rendered free to pass through a semipermeable membrane.<sup>20</sup> At the same time caeruloplasmin loses its oxidase activity and the blue color is discharged.

It might, with justification, be argued that these observations, while of great theoretical interest in furthering our understanding of copper transport and mobilization, are of little value to clinical medicine. However, this is far from the case. Long term therapeutic trials in which penicillamine has been given for months or years leave no room for doubt as to its value in the treatment of Wilson's disease. The largest series so far collected by Walshe and collaborators<sup>21</sup> showed that 17 out of 22 patients with Wilson's disease were improved, some dramatically, and only three failed to benefit; two were treated in the presymptomatic stage of the disease.

<sup>17</sup> Osborn, S. B., and Walshe, J. M.: Effects of penicillamine and dimercaprol on turnover of copper in patients with Wilson's disease, *Lancet* 1: 70, 1958.

<sup>18</sup> Hill, L. E., and Walshe, J. M.: The action of chelating agents in Wilson's disease, *Lancet* 2: 444, 1959.

<sup>19</sup> Walshe, J. M.: *Clinical Science*. In press.

<sup>20</sup> Walshe, J. M.: Studies on the action of penicillamine, in *Metal Binding in Medicine*, J. B. Lippincott Company, Philadelphia, 1960, page 265.

<sup>21</sup> Walshe, J. M.: Treatment of Wilson's disease with penicillamine, *Lancet* 1: 188, 1960.



In a smaller series, but with more detailed biochemical control, Scheinberg<sup>22</sup> has had similarly encouraging results.

While no serious toxicity has been observed with the use of D-penicillamine, prepared from penicillin, administration of the synthetic DL penicillamine has been associated with some toxic reactions. The most serious of these has been granulocytopenia<sup>22, 23</sup> and fever. If it is safe to argue from the experimental animal to man the addition of pyridoxine to the regimen should eliminate these dangers which are probably due to the anti-B<sub>6</sub> action of L-penicillamine.

It was originally suggested that penicillamine should be of value not only for mobilizing copper from patients with Wilson's disease but also in the treatment of other heavy metal intoxications<sup>2</sup>; mercury, lead, gold and iron spring to mind. Boulding and Baker<sup>24</sup> and Harris<sup>25</sup> have each reported good mobilization of lead in two cases of inorganic lead poisoning, but Boyd, Williams and Henderson<sup>26</sup> observed no benefit in tetraethyl lead intoxication. Iron deposited in the tissues in hemochromatosis and hemosiderosis did not appear to be mobilized by penicillamine<sup>24</sup> but a trial of this compound in ferrous sulphate poisoning in children would appear to be justified. The use of penicillamine in mercury intoxication also deserves attention. Aposhian<sup>27, 28</sup> has shown that D-penicillamine affords excellent protection against the lethal effect of mercuric chloride poisoning in rats although the L isomer was found to be inactive in these studies. Even more active, he found, was N-acetyl DL-penicillamine, but unfortunately he quotes no figures for mercury excretion in the urine in his animals. Acetyl penicillamine has been tried as a cupruritic in man and found to be inactive.<sup>29, 30</sup> In view of Aposhian's work just quoted it would be interesting to know if it had any beneficial action in the treatment of Wilson's disease despite its apparent failure to mobilize copper.

Mention must also be made here of a somewhat unexpected and hitherto unexplained property of penicillamine: that is its ability to reduce viscosity and gel formation in the sera of patients with Waldenström's macroglobulinemia. These physical changes in the proteins are associated with

<sup>22</sup> Scheinberg, I. H., and Sternlieb, I.: The long-term management of hepatolenticular degeneration (Wilson's disease), *Amer. J. Med.* **24**: 316, 1960.

<sup>23</sup> Walshe, J. M.: Current views on the pathogenesis and treatment of Wilson's disease, *A. M. A. Arch. Int. Med.* **103**: 155, 1959.

<sup>24</sup> Boulding, J. E., and Baker, R. A.: The treatment of metal poisoning with penicillamine, *Lancet* **2**: 985, 1957.

<sup>25</sup> Harris, C. E. C.: A comparison of intravenous calcium disodium versenate and oral penicillamine in promoting elimination of lead, *Canad. M. A. J.* **79**: 664, 1958.

<sup>26</sup> Boyd, P. R., Walker, G., and Henderson, I. N.: The treatment of tetraethyl lead poisoning, *Lancet* **1**: 181, 1957.

<sup>27</sup> Aposhian, H. V.: Protection by D-penicillamine against the lethal effects of mercuric chloride, *Science* **128**: 93, 1958.

<sup>28</sup> Aposhian, H. V., and Aposhian, M. M.: N-Acetyl DL-penicillamine, a new oral protective agent against the lethal effects of mercuric chloride, *J. Pharmacol.* **126**: 131, 1959.

<sup>29</sup> Scheinberg, I. H.: Personal communication.

<sup>30</sup> Walshe, J. M.: Unpublished observations.

clinical remission which may last several weeks after the drug has been discontinued.<sup>31, 32</sup>

One final speculation on the pharmacological actions of penicillamine might be permitted before closing this review. Sulphdryl compounds are known to protect against the lethal effects of ionizing radiations and among the most active of these is cysteamine<sup>33</sup> but, like BAL, this has the disadvantage that it must be given parenterally. It would be a great advance if a compound such as penicillamine, which can be given by mouth, proved to be active in this field. On the other hand its relative stability and metabolic inertness, so important for its chelating properties, might render it of little use for radiation protection.

J. M. WALSHE

<sup>31</sup> Bloch, H. S., Prasad, A., and Anastasi, A.: Serum protein changes in Waldenstrom's macroglobulinaemia during penicillamine administration, *Proc. Cent. Soc. Clin. Res.* **31**: 12, 1958.

<sup>32</sup> Ritzmann, S. E., Thurm, R. H., Truax, W. E., and Levin, W. C.: The syndrome of macroglobulinemia, *A. M. A. Arch. Int. Med.* **105**: 939, 1960.

<sup>33</sup> Bacq, Z. M., Dechamps, G., Fischer, P., Herve, A., le Bihan, H., Lecomte, J., Pirotte, M., and Rayet, P.: Protection against X-rays and therapy of radiation sickness with  $\beta$ -mercaptoethyamine, *Science* **117**: 633, 1953.

## BOOK REVIEWS

*Diabetes, with a Chapter on Hypoglycemia.* By 54 authors; edited by ROBERT H. WILLIAMS, M.D., Executive Officer and Professor of Medicine, University of Washington, Physician-in-Chief, University Hospital, Seattle. 793 pages; 24 × 16 cm. Paul B. Hoeber, Inc., Medical Division of Harper Brothers, New York, N. Y. 1960. Price, \$20.00.

The editor's preface accurately describes the book. Quotation of its first two paragraphs will permit the reader of this review to decide upon its purchase.

"The recent tremendous progress in many facets of research dealing with metabolic changes in diabetes and its concomitants (complications) prompted the writing of this book for scientists with varied interests, but particularly for internists, basic medical scientists, and students. It is a unique condensation of the latest and most authoritative information at both the basic science and clinical levels, written in a clear and straightforward manner by more than 40 experts from widely dispersed areas of the world. The authors were selected not only on the basis of their outstanding research contributions but also for their demonstrated effectiveness as teachers and authors. The editor made special efforts to attain coordination of the discussions throughout this book. Some repetition is unavoidable and, indeed, desirable. In attaining conciseness, we have dwelt lightly on controversial issues and on unimportant diagnostic and therapeutic procedures. We have put much more emphasis upon new information than old. While presenting the accumulated knowledge, we have attempted to impart understanding by indicating how basic scientific observations apply to clinical problems. Many figures and tables are used for illustrations. Most chapters contain summaries of the important conclusions. A limited number of selected references are included.

"Following an interesting discussion by Dr. Charles Best of major epochs in the history of diabetes, there are presented descriptions of the chemistry of insulin, its secretion, its distribution throughout the body, and its fate as well as its role in carbohydrate, fat, and protein metabolism. There also is consideration of allied actions of other hormones, particularly glucagon, epinephrine, corticosteroids, and growth hormone. The effect of these hormones on insulin responsiveness and the stabilization of carbohydrate metabolism is stressed. Factors are described in the serum which are antagonistic to insulin, accounting for marked insulin resistance. Many aspects of the etiology, pathogenesis, pathology, clinical manifestations, and diagnosis of diabetes are discussed. There is extensive consideration of the clinical management of diabetes, including the use of general hygienic measures, diet, insulin, and oral antidiabetic agents. Meticulous attention is given to a discussion of the most recent and extensive investigations dealing with tolbutamide, chlorpropamide, metahexamide, phenethylbiguanide, and other oral antidiabetic compounds. Several chapters are devoted to major concomitants of diabetes and to different types of diabetes. The special problems of diabetes in children and during pregnancy are discussed in individual chapters. Extensive attention is given to the problem of hypoglycemia, including consideration of its many causes, damaging effects, diagnosis, and therapy."

Although each chapter follows another in a logical plan, each can be read as a separate monograph. Only four are longer than 30 pages—those on diagnostic tests in diabetes mellitus (Fajans), oral hypoglycemic agents (Williams), diabetic acidosis (Daughaday), and hypoglycemia (Williams). Absent are discussion of most of the technical details related to patient instruction in insulin administration, cautions about the menace of the double scale insulin syringe as a cause of hyperinsulinism and hypoglycemia as well as acidosis, mention of U-500 insulin as an aid in the

management of insulin-resistant patients by reduction in dosage volume. A single arithmetic error was noted: on page 428, 230 is not 70% below 340 but only 30% below.

This book can be read by internists with pleasure as well as profit. It should be readily available to all physicians treating patients with diabetes mellitus.

PERRY FUTTERMAN

*Modern Scientific Aspects of Neurology.* Edited by JOHN M. CUMINGS, M.D., F.R.C.P. 360 pages; 23.5 × 15.5 cm. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. 1960. Price, \$13.00.

This small volume of 360 pages contains 10 chapters, each by a different contributor. The emphasis is on the basic science aspects of the nervous system but with the greatest emphasis on neurochemistry. Each chapter is the contribution of a separate individual—including investigators from England, Belgium, Germany, Denmark, Austria and Sweden.

It is evident that the book is designed for the clinician working in neurology. Each contributor is careful to acquaint the reader with the technics of investigation used in obtaining the data which he presents. In addition, there is in each chapter a good review of the literature relative to the subject under discussion. The first chapter on nucleic acids discusses at some length the histochemical methods used in studying nucleic acids. The second chapter on nerve endings in striated muscle also describes in some detail the histochemical technics which have been utilized in the study of such structures, as well as the data which have been obtained with such technics.

The third chapter is concerned with a histochemical study of the lipoidoses, while the chapter contributed by the editor presents chemical analyses of brain material in these diseases and in the demyelinating diseases. In this latter chapter the author points out the value of cerebral biopsy and reviews his experience with such material. Other chapters are concerned with electron microscopy of nervous tissue, x-ray diffraction study of myelin, as well as other chemical aspects of the nervous system, both normal and in disease states. One chapter is a review of the chemical and physiologic data available on convulsive disorders.

Since each chapter is in the nature of a review article, it is followed by a quite complete bibliography. In addition, there is a useful index at the end of the volume.

This book was designed for the clinician and will be of particular value in helping him keep current with the newer basic science developments concerning the nervous system and in acquainting him with the technics used. In this age of specialization it should be of interest to basic scientists as well. The trainee in clinical neurology and neurosurgery will find this volume a good review. In this reader's opinion this small book is a very worthwhile addition to the library of clinicians concerned with the nervous system. The contributors have made a valuable contribution in reviewing the material involved and in presenting it in such a fashion that the clinician can appreciate and understand it.

C. VAN BUSKIRK

*Medical Care of the Adolescent: A Textbook Concerning the Medical Care and Understanding of Adolescents Themselves and of Their Disorders.* By J. ROSWELL GALLAGHER, M.D., Chief of the Adolescent Unit, The Children's Hospital Medical Center, Boston, and the Staff Physicians of the Adolescent Unit. 384 pages; 24 × 16 cm. Appleton-Century-Crofts, Inc., New York. 1960. Price, \$10.00.

From his long and varied experience in dealing with young people, Dr. Gallagher has written a book that fills a void. It merits the attention and interest of all

physicians—especially the pediatrician, the general practitioner, and the internist. Many of the topics discussed have been the subject of papers contributed by the author to various medical journals, but are now organized into a single compact volume.

Recognition of the adolescent as wandering in a "no man's land" and looking for help and counsel is stressed as fundamental to a proper relationship between patient and physician. A deep sympathetic understanding of the teenager's needs, his psychological and emotional problems, is emphasized. Variations in growth and development are adequately covered. Organic illness is explored on a sound basis. Several chapters are devoted to problems peculiar to the adolescent's school failures. Athletic injuries are discussed; and the prevention of accidents—so common in this day of hot-rodding.

J. F.

*Communicable and Infectious Diseases: Diagnosis, Prevention, Treatment.* 4th Ed.

By FRANKLIN H. TOP, A.B., M.D., M.P.H., F.A.C.P., F.A.A.P., F.A.P.H.A., and collaborators. 812 pages; 25.5 × 17 cm. The C. V. Mosby Co., St. Louis. 1960. Price, \$20.00.

This volume, a fourth edition, offers a complete reference in the field of practical infectious diseases. A number of investigators, all authorities in various aspects of infectious diseases, serve as contributing authors. This edition correlates well with changing trends in infectious diseases as demonstrated by new chapters devoted to the subjects of acute viral respiratory infections, enterovirus infections and emphasis on the problem of staphylococcal infections as well as current concepts pertaining to the use of antimicrobial drugs.

Most of the chapters are devoted to discussion of various disease entities with major emphasis upon clinical characteristics, such as symptoms, differential diagnosis, prognosis, and treatment, including nursing care and prevention. Although information concerning the biologic characteristics of the infectious agent is sparse, a rather complete and current list of references accompanies each chapter.

This is a well written and readable volume providing current information in the field of infectious diseases. It is written primarily for the practicing clinician and is recommended as a reference volume for all persons involved in the care of individuals ill with communicable diseases. Because of special emphasis on communicability and nursing care this volume is especially recommended as a reference for nurses.

L. J. M.

*Your Heart: A Handbook for Laymen.* By H. M. MARVIN, M.D. 335 pages; 21.5 × 14.5 cm. Doubleday & Company, Inc., Garden City, New York. 1960. Price, \$4.50.

The author of this book, H. M. Marvin, M.D., has served as President of the American Heart Association. In the Introduction, he states, "This book was written in the hope that it might bring clearer understanding of the heart's function and disorders to nonmedical readers. Some may be interested because they have heart disease; others might suspect the existence of such disease because of symptoms that are actually quite innocent."

This book is not an outline; nor is it brief. Its contents range from a detailed description of the anatomy of the heart, to irregularities in rhythm; from causes of coronary atherosclerosis to anticoagulants; from the heart in pregnancy to congenital malformations. There is little of importance omitted in this tightly written text of some 335 pages. It is a highly factual presentation with controversial as well as established opinions included. The author freely expresses his own ideas on

methods of treatment and diagnosis. As the author explains, "Inasmuch as this book is essentially an expression of my own beliefs and practices, based upon personal experiences and the reported experiences of others, it seems fitting that this chapter should conclude with a brief expression of my opinion." The available literature is selectively quoted, and there is a useful glossary.

The reviewer questions whether the text serves its avowed purpose to bring understanding and comfort to the many affected with heart disease. Many of the discussions are prolonged, extremely controversial, and the final conclusions often subject to disagreement by other competent cardiologists. A cardiac patient is hardly comforted by reading recommendations for treatment at variance with those actually instituted in his case. A cardiac book for the layman can be of value, but this text appears more suitable for the scientifically oriented reader educated to sift and evaluate experimental and conflicting data. It should prove of value for science editors, medical students, nurses, and those readers in allied fields.

LEONARD SCHERLIS, M.D.

*Basic Facts of Body Water and Ions.* By STEWART M. BROOKS, M.S. 159 pages; 21 x 14 cm. (paper-bound). Springer Publishing Co., Inc., New York. 1960. Price, \$2.75.

Written for beginners in the area of application of chemistry to human physiology, particularly students of nursing, pharmacy, and medical technology, this brief volume touches the important parts of this field. The book is divided into three stages. Part One covers the basic concepts of solutions, ions, and acid-base balance. Part Two applies these concepts to clinical conditions including parenteral maintenance, edema, renal failure, and imbalances. Part Three is a glossary of terms used, a brief bibliography, and an index.

Many of the definitions are succinctly good, with no pretense to completeness or strictness, they are pragmatic and utilitarian. Presumably such an approach best suits the novice. The style has an awakening quality, approaching the "bed time story" manner at times, but seldom using a short word when a long one will do. The illustrations are simplified and clear, as are most examples cited in the text. The volume can be helpful to beginning students.

C. B. A.

*Dermatologic Medications.* 2nd Ed. By MARGUERITE RUSH LERNER, M.D., and AARON BUNSEN LERNER, M.D., Ph.D. 208 pages; 20.5 x 13.5 cm. The Year Book Publishers, Inc., Chicago. 1960. Price, \$6.00.

This book, written by eminently qualified teachers of dermatology, is an excellent up to date treatise on the treatment of conditions characterized by cutaneous lesions. The authors have written a carefully constructed text in which they not only give generic names and trade names but also structural formulae for the various drugs. The pharmacologic action of the various preparations is presented in capsule form which enhances the value of the text to graduate students in dermatology as well as to general practitioners. The text is not opinionated.

Although in most areas the authors have mentioned the sensitizing potential of various preparations applied topically, they neglect to mention the sensitizing properties of the various germastatic soaps.

This text is recommended without reservation for inclusion in the libraries of dermatologists, students in training, and general practitioners.

H. M. R., Jr.



*Clinical Physiology. Volume One: Electrolyte Balance, Water Metabolism, Renal Function, Gastro-intestinal Function, Hepatic Failure.* By KATHLEEN E. ROBERTS, M.D., Director of Research, U. S. Public Health Service Hospital, San Francisco. 226 pages; 23.5 × 15.5 cm. Filmer Publishing Co., San Francisco. 1960. Price, \$6.50.

Although there is much valuable material in this book, and although Dr. Roberts certainly knows a great deal about the various subjects considered, the text does not at all fulfill her stated objectives: "To emphasize fundamentals rather than complicated dogmas and rules, for students and novices rather than specialists in the field." On the contrary, the presentation is quite detailed; for the non-specialist the subject certainly is complicated; and, since the points of view are only rarely documented with references to the source of the information presented, one must either accept the author's dogmatic statements or ignore them entirely.

In view of this, it needs emphasis that all of the book cannot be taken literally. To name a few points where I differ with the author: Van Slyke, not Gamble, first used block diagrams to describe anion-cation patterns in body fluids; elevation of blood ammonia does not result in hyperventilation; the numerator of the Henderson-Hasselbach equation is  $\text{HCO}_3^-$  not  $\text{BHCO}_3$ , the pH difference between reduced and oxygenated blood is due to the fact that the pK value of reduced hemoglobin is higher than the pK value of oxygenated hemoglobin—not because reduced hemoglobin is the "more alkaline substance"; novices, especially novices, should be presented with the newer concepts of acid-base terminology rather than the older parlance.

In spite of my generally unfavorable reaction to the book, many who are somewhere between novice and expert can read it to advantage—largely because of the author's willingness to present her interpretations of difficult and controversial subjects without hesitation.

B. W. A.

#### BOOKS RECENTLY RECEIVED

Books recently received are acknowledged in the following section. As far as practicable those of special interest will be selected for review later, but it is not possible to discuss all of them.

*Acute Conditions: Incidence and Associated Disability, United States, July 1958–June 1959. Statistics on Incidence of Acute Conditions and Number of Associated Restricted-Activity Days, Bed-Days, Work-Loss Days, and School-Loss Days According to Condition Group. Based on Data Collected in Household Interviews During the Period July 1958–June 1959. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584-B18.* 34 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 30¢.

*Advances in Internal Medicine. Volume X, 1960.* Editors: WILLIAM DOCK, M.D., State University of New York College of Medicine at New York City; and I. SNAPPER, M.D., Beth-El Hospital, Brooklyn. 390 pages; 23.5 × 15 cm. 1960. The Year Book Publishers, Inc., Chicago. Price, \$10.50.

*Cardiac Emergencies and Related Disorders: Their Mechanism, Recognition and Management.* By HAROLD D. LEVINE, M.D., Senior Associate in Medicine, Peter Bent Brigham Hospital, Boston, Mass., etc. 381 pages; 23.5 × 15.5 cm. 1960. Landsberger Medical Books, Inc., New York. Price, \$12.00.

- Cellular Aspects of Immunity. Ciba Foundation Symposium.* Editors for the Ciba Foundation: G. E. W. WOLSTENHOLME, O.B.E., M.A., M.B., M.R.C.P.; and MAEVE O'CONNOR, B.A. 495 pages; 21 × 14 cm. 1960. Little, Brown and Company, Boston. Price, \$10.50.
- The Child with Mongolism (Congenital Acromicria).* By CLEMENS E. BENDA, M.D., Director of Research and Psychiatry, Walter E. Fernald State School, Waverley, Massachusetts, etc. 276 pages; 23.5 × 15.5 cm. 1960. Grune & Stratton, New York. Price, \$9.50.
- Clinical Chemistry: Principles and Procedures.* 2nd Ed. By JOSEPH S. ANNINO, Clinical Chemist, Massachusetts Memorial Hospitals, Boston, Massachusetts. 348 pages; 24 × 16 cm. 1960. Little, Brown and Company, Boston. Price, \$8.00.
- The Clinical Use of Aldosterone Antagonists.* Compiled and Edited by FREDERIC C. BARTER, with 23 contributors. 211 pages; 23.5 × 15.5 cm. 1960. Charles C Thomas, Springfield, Illinois. Price, \$5.00.
- Cold Injury: Transactions of the Sixth Conference, July 6, 7, 8, 9, and 10, 1958, U. S. Army Medical Research Laboratory, Fort Knox, Ky.* Edited by STEVEN M. HORVATH, M.S., Ph.D., Division of Research, Lankenau Hospital, Philadelphia, Pa. 375 pages; 23.5 × 16 cm. 1960. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$6.50.
- Coöperation in Health Examination Surveys: A Study of Expressed Willingness to Accept a Health Examination for Survey Purposes. Health Statistics from the U. S. National Health Survey. Public Health Service Publication No. 584-D2.* 38 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Printing Office, Washington 25, D. C., at 35¢.
- Demonstrations of Physical Signs in Clinical Surgery.* 13th Ed. By HAMILTON BAILEY, F.R.C.S. (Eng.), F.A.C.S., F.R.S.E., Emeritus Surgeon, Royal Northern Hospital, London, etc. 928 pages; 22.5 × 14.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$14.50.
- Diagnostic Roentgenology of the Digestive Tract without Contrast Media. A Mount Sinai Hospital Monograph.* By BERNARD S. WOLF, M.D., Director, Department of Radiology, The Mount Sinai Hospital, New York, etc.; MANSHO T. KHILOANI, M.B., Associate Fellow in Radiology, The Mount Sinai Hospital, New York; and ARTHUR LAUTKIN, M.D., Associate Radiologist, The Mount Sinai Hospital, New York, etc. 180 pages; 26 × 17.5 cm. 1960. Grune & Stratton, New York. Price, \$8.75.
- Endemic Goitre. World Health Organization Monograph Series No. 44.* Contributors: F. W. CLEMENTS, J. DE MOERLOOSE, M. P. DE SMET, J. C. M. HOLMAN, F. C. KELLY, P. LANGER, S. LISSITZKY, F. W. LOWENSTEIN, W. MCCARTNEY, J. MATOVINOVIĆ, S. T. MILCU, J. A. MUÑOZ, C. PEREZ, V. RAMALINGASWAMI, J. ROCHE, N. S. SCRIMSHAW, W. W. SNEDDEN and J. B. STANBURY. 481 pages; 24 × 16 cm. 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$8.00.
- European Technical Conference on the Control of Infectious Diseases Through Vaccination Programmes, Rabat, Morocco, 23-31 October 1959: Report. World*

- Health Organization Technical Report Series No. 198.* 21 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 30¢.
- Expert Committee on Venereal Infections and Treponematoses: Fifth Report. World Health Organization Technical Report Series No. 190.* 73 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, \$1.00.
- French's Index of Differential Diagnosis.* 8th Ed. Edited by ARTHUR H. DOUTHWAITE, M.D., F.R.C.P., Senior Physician, Guy's Hospital, etc. 1,111 pages; 25.5 × 16.5 cm. 1960. The Williams & Wilkins Co., Baltimore, exclusive U. S. agents. Price, \$24.00.
- Fundamentals of Nerve Blocking.* By VINCENT J. COLLINS, M.S., M.D., Associate Professor of Anesthesiology, New York University Medical Center and Anesthesiologist, Bellevue Hospital Center; with the assistance of EMERY ANDREW ROVENSTINE, M.D., Professor of Anesthesiology and Chairman of Department of Anesthesiology, New York University Medical Center and Director Division of Anesthesia, Bellevue Hospital Center. 354 pages; 24 × 15.5 cm. 1960. Lea & Febiger, Philadelphia. Price, \$9.50.
- Geriatric Nursing.* 3d Ed. By KATHLEEN NEWTON, R.N., M.A., formerly Associate Professor in Out-Patient Nursing, The Cornell University-New York Hospital School of Nursing, New York, N. Y., etc. 483 pages; 22.5 × 14.5 cm. 1960. The C. V. Mosby Company, St. Louis. Price, \$6.50.
- Les Globulines Sériques du Système Gamma: Leur Nature et Leur Pathologie.* By J. HEREMANS; preface by PROFESSEUR P. GRABAR. 340 pages; 24 × 16 cm. (paper-bound). 1960. Editions Arscia S. A., Brussels. Price, 690 Fr. belges.
- Group Processes: Transactions of the Fifth Conference October 12, 13, 14, and 15, 1958, Princeton, N. J.* Edited by BERTRAM SCHAFFNER, M.D., University Seminar on Communications, Columbia University, New York, N. Y. 196 pages; 24 × 16 cm. 1960. Sponsored by the Josiah Macy, Jr. Foundation, New York. Price, \$4.50.
- The Human Blood Proteins: Methods of Examination and Their Clinical and Practical Significance.* By PROF. FERDINAND WUHRMANN, M.D., and CHARLIE WUNDERLY, Ph.D.; translation from the third and completely revised edition by HARVEY T. ADELSON, M.D. 489 pages; 24.5 × 17.5 cm. 1960. Grune & Stratton, New York. Price, \$15.75.
- Illusions and Delusions of the Supernatural and the Occult (The Psychology of the Occult).* By D. H. RAWCLIFFE. 551 pages; 20.5 × 13.5 cm. (paper-bound). 1960 (New Dover edition, first published in 1959, an unabridged and unaltered republication of the first edition of the work originally published under the title of *The Psychology of the Occult*). Dover Publications, Inc., New York. Price, \$2.00.
- Immunization Information for International Travel.* Prepared by the EPIDEMIOLOGY AND DOMESTIC OPERATIONS BRANCH, DIVISION OF FOREIGN QUARANTINE OF THE BUREAU OF MEDICAL SERVICES, UNITED STATES PUBLIC HEALTH SERVICE. 83 pages; 11.5 × 15 cm. (paper-bound). 1960. U. S. Department of Health, Edu-

cation, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 25¢. (Discount of 25% for 100 or more copies delivered to same address.)

*Joint FAO/WHO Expert Committee on Milk Hygiene: Second Report. World Health Organization Technical Report Series No. 197.* 55 pages; 24 × 16 cm. (paper-bound). 1960. World Health Organization, Geneva; available in U. S. A. from Columbia University Press, International Documents Service, New York. Price, 60¢.

*Krebiozen, Fact and Fiction: A Compilation of Pertinent Documents.* 36 pages; 28 × 21.5 cm. (paper-bound). 1960. Citizens Emergency Committee for Krebiozen, Rhoda Boyco, Acting Chairman, New York. Price, \$1.00.

*Das Menschliche Knochenmark: Anatomie, Physiologie und Pathologie Nach Ergebnissen der Intravitalen Marpunktion.* By PROF. DR. MED KARL ROHR. 593 pages; 25 × 17.5 cm. 1960. Georg Thieme Verlag, Stuttgart. Price, Ganzleinen DM 98.-

*Quantitative Paper Chromatography of Steroids: Proceedings of a Conference Held at the Ciba Foundation, London, W.1, on 1 July 1958. Memoirs of the Society for Endocrinology No. 8.* Edited on behalf of the Society for Endocrinology by D. ABELSON and R. V. BROOKS. 103 pages; 25 × 19 cm. 1960. Cambridge at the University Press. Price, \$6.00.

*Renal, Electrolyte and Autonomic Factors (Volume VIII of Hypertension): Proceedings of the Council for High Blood Pressure Research, American Heart Association, November, 1959.* Edited by FLOYD R. SKELTON, M.D., Ph.D., Research Director, The Urban Maes Research Foundation and Associate Professor of Pathology, Louisiana State University School of Medicine, New Orleans, La. 150 pages; 23 × 15.5 cm. 1960. American Heart Association, New York. Price, \$2.75.

*Selwyn D. Collins' Contributions to Health Statistics: A Guide to His Works. Public Health Monograph No. 62. Public Health Service Publication No. 737.* 14 pages; 26 × 20 cm. (paper-bound). 1960. U. S. Department of Health, Education, and Welfare, Public Health Service, Washington, D. C. For sale by the Superintendent of Documents, U. S. Government Printing Office, Washington 25, D. C., at 20¢.

*St. Peter's Hospital for Stone, 1860-1960.* Edited by CLIFFORD MORSON, O.B.E., F.R.C.S. 64 pages; 25.5 × 18.5 cm. 1960. The Williams & Wilkins Company, Baltimore, exclusive U. S. agents. Price, \$5.00.

*Symposium on Congestive Heart Failure. American Heart Association Monograph Number One.* (Originally published and copyrighted in *Circulation*, January, February, March, 1960.) Edited by HERRMAN L. BLUMGART, M.D., Professor of Medicine, Harvard Medical School, etc. 120 pages; 26 × 19 cm. (paper-bound). 1960. American Heart Association, Inc., New York. Price, \$2.00.

*Symposium on Salt and Water Metabolism.* (Originally published as a supplement of *Circulation*: Vol. XXI, No. 5, Part 2, May 1960.) ALFRED P. FISHMAN, M.D., Guest Editor. 255 pages; 27.5 × 20 cm. (paper-bound). 1960. American Heart Association-New York Heart Association, New York. Price, \$2.00 postpaid, available from either the New York Heart Association or the American Heart Association.

## MEDICAL NEWS

### MEETINGS

- Dec. 3-8, 1960 AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY, Palmer House, Chicago, Dec. 3-8. Dr. Robert R. Kierland, First National Bank Bldg., Rochester, Minn., Secretary-Treasurer.
- Dec. 9, 1960 AMERICAN RHEUMATISM ASSOCIATION, Sheraton Dallas Hotel, Dallas, Texas, Dec. 9. Mr. Gerard W. Speyer, 10 Columbus Circle, New York 19, Executive Secretary.
- Dec. 1-2, 1960 CONFERENCE ON GRADUATE MEDICAL EDUCATION—"EDUCATIONAL PROBLEMS IN THE INTERNSHIP AND RESIDENCY," University of Pennsylvania Graduate School of Medicine, Dec. 1-2. For information write Dr. Paul Nemir, Jr., 237 Medical Laboratories Bldg., Philadelphia 4, Dean.
- Dec. 9-10, 1960 NEW YORK HEART ASSOCIATION, SYMPOSIUM ON THE MYOCARDIUM, ITS BIOPHYSICS AND BIOCHEMISTRY, Waldorf-Astoria Hotel, New York City, Dec. 9-10. For information write Dr. Alfred P. Fishman, N. Y. Heart Ass'n., 10 Columbus Circle, New York 19.
- Dec. 4-9, 1960 RADIOLOGICAL SOCIETY OF NORTH AMERICA, Netherland Hilton Hotel, Cincinnati, Dec. 4-9. Dr. Donald S. Childs, 713 E. Genesee St., Syracuse 2, N. Y., Secretary.
- Dec. 8, 1960 SOCIETY OF BIOLOGICAL PSYCHIATRY, Hotel Roosevelt, New York City, Dec. 8. Dr. George N. Thompson, 2010 Wilshire Blvd., Los Angeles 57, Secretary.
- Dec. 25-Jan. 16, 1961 BAHAMAS MEDICAL CONFERENCE, Nassau, Bahamas. Dr. B. L. Frank, P. O. Box 4037, Fort Lauderdale, Fla.
- Jan. 7, 1961 NORTHWEST SOCIETY FOR CLINICAL RESEARCH, Hotel Georgia, Vancouver, B. C., Canada, Jan. 7. Dr. John R. Hogness, University Hospital, Seattle, Secretary-Treasurer.
- Feb. 6-8, 1961 AMERICAN ACADEMY OF ALLERGY, Statler-Hilton Hotel, Washington, D. C., Feb. 6-8. Mr. James O. Kelley, 756 N. Milwaukee St., Milwaukee, 2, Wis., Executive Secretary.
- Feb. 8-11, 1961 AMERICAN COLLEGE OF RADIOLOGY, Drake Hotel, Chicago, Feb. 8-11. William C. Stronach, LL.B., 20 N. Wacker Drive, Chicago 6, Executive Director.
- Feb. 4-7, 1961 CONGRESS ON MEDICAL EDUCATION AND LICENSURE, Palmer House, Chicago, Feb. 4-7. For Information write Mrs. Ann Tipner, A. M. A., 535 N. Dearborn St., Chicago 10.

- Mar. 12-17, 1960 AMERICAN COLLEGE OF ALLERGISTS, Statler Hilton, Dallas, Texas, Mar. 12-17. Dr. Howard G. Rapaport, 16 E. 79th St., New York City, Secretary.
- Mar. 13-16, 1961 NATIONAL HEALTH COUNCIL, NATIONAL HEALTH FORUM, "HEALTH AND COMMUNICATION," Waldorf-Astoria, New York City, Mar. 13-16. Mr. Philip E. Ryan, 1790 Broadway, New York 19, Executive Director.
- Apr. 10-12, 1961 AMERICAN ACADEMY OF PEDIATRICS, spring meeting, Sheraton-Park Hotel, Washington, D. C., Apr. 10-12. For information write Dr. E. H. Christopherson, 1801 Hinman Ave., Evanston, Ill., Executive Director.
- Apr. 26-29, 1961 AMERICAN COLLEGE HEALTH ASSOCIATION, Detroit, Apr. 26-29. Dr. Norman S. Moore, Cornell University, Gannett Clinic, Ithaca, N. Y., Secretary-Treasurer.
- Apr. 27-28, 1961 EASTERN STATES HEALTH EDUCATION CONFERENCE, New York Academy of Medicine, Apr. 27-28. For information write Dr. Iago Galdston, New York Academy of Medicine, 2 E. 103 St., New York City.
- Apr. 30, 1961 AMERICAN FEDERATION FOR CLINICAL RESEARCH, Haddon Hall, Atlantic City, Apr. 20. James E. Bryan, 250 W. 57th St., New York 19, Executive Secretary.

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#### POSTGRADUATE COURSES

##### THE AMERICAN COLLEGE OF PHYSICIANS

###### SCHEDULE OF POSTGRADUATE COURSES, AUTUMN-WINTER, 1960-61

- Jan. 9-13, 1961 Course No. 4, RECENT ADVANCES IN DRUG THERAPY: University of Washington School of Medicine, Seattle, Wash., Robert H. Williams, M.D., F.A.C.P., Director.
- Jan. 16-20, 1961 Course No. 5, MECHANISMS OF DISEASE: Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.
- Feb. 20-24, 1961 Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE: The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.
- Spring, 1961 The following courses are scheduled for Spring, 1961: CARDIOVASCULAR DISEASES, Mount Sinai Hospital, Charles K. Friedberg, M.D., F.A.C.P., Director, March 6-10;



INTERNAL MEDICINE, McGill University, Ronald V. Christie, M.D., F.A.C.P., Director, March 13-17;

ADVANCED CLINICAL ELECTROCARDIOGRAPHY, The University of Tennessee, I. Frank Tullis, M.D., F.A.C.P., Director, March 20-24;

ENDOCRINOLOGY, University of Virginia, William Parson, M.D., F.A.C.P., Director, March 23-25;

PROBLEMS OF GROWTH AND AGING, Lankenau Medical Building, Philadelphia, Edward L. Bortz, M.D., F.A.C.P., Director, April 12-15;

GASTROENTEROLOGY, University of Pennsylvania School of Medicine; Henry L. Bockus, M.D., F.A.C.P., Director, May 15-19;

CURRENT ASPECTS OF INTERNAL MEDICINE, State University of Iowa, William B. Bean, M.D., F.A.C.P., Director, June 19-23.

Three Months:  
Feb. 1-Apr. 29, 1961

CARDIOLOGY: Louis Wolff, M.D., and Associates at the Beth Israel Hospital. Tuition: \$500. For further information, write: Ass't. Dean, Courses for Graduates, Harvard Medical School, Boston 15, Mass.

Mar. 27-31, 1961

THE MEASUREMENT OF PULMONARY FUNCTION IN HEALTH AND DISEASE: Boston City Hospital, Boston, Mass. Tuition: \$100. (\$75 for members of the American Thoracic Society.) Applications should be directed to: Edward J. Welch, M.D., F.A.C.P., Chairman of Course, 1101 Beacon Street, Brookline, Mass.

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#### EXAMINATIONS

##### AMERICAN BOARD OF PHYSICAL MEDICINE AND REHABILITATION

The next examinations, written and oral, of the American Board of Physical Medicine and Rehabilitation will be held in New York City, June 24 and 25, 1961. THE FINAL DATE FOR SUBMITTING APPLICATIONS IS FEBRUARY 15, 1961.

##### AMERICAN BOARD OF NUTRITION

The American Board of Nutrition will hold the next examinations for certification as a Specialist in Human Nutrition on Monday, April 10, 1961, in Atlantic City. Candidates who wish to be considered for these examinations should forward applications to the Secretary's office not later than March 1. Application forms may be obtained from the Secretary, Robert E. Shank, M.D., Department of Preventive Medicine, Washington University School of Medicine, Euclid and Kingshighway, St. Louis, Missouri.

## FELLOWSHIPS

## FELLOWSHIPS IN INDUSTRIAL MEDICINE

The U. S. Atomic Energy Commission announces special Fellowships in Industrial Medicine for the academic year, 1961-62. Eight Fellowships will be available and inquiries should be addressed to:

A.E.C. Fellowships in Industrial Medicine,  
Atomic Energy Project,  
University of Rochester  
School of Medicine and Dentistry,  
Rochester 20, New York  
Attn: Dr. Henry A. Blair

## FELLOWSHIP REPORT AVAILABLE

The National Health Council announces that facts about Fellowships for health research are now available in a single report. Based on a meeting of the Council's Committee on Research, the report contains information about fellowship and traineeship programs of federal and non-governmental agencies.

Copies may be purchased for \$1.00 from the National Health Council, 1790 Broadway, New York 19, N. Y.

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ECG inputs in conjunction with other equipment. The cabinet is available in either handsome mahogany or exceptionally durable, stain-resistant plastic laminate.

The same basic instrument — with identical circuitry — is also manufactured as a desk-top instrument, designated Model 100 Viso-Cardiette. A third choice in Sanborn ECG'S is also offered, for the physician whose practice demands *maximum portability*: the 18-pound "briefcase" size Model 300 Visette. All are proven Sanborn electrocardiographs, reflecting more than four decades of experience in the manufacture of medical instrumentation.

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Think, too, of the night: the state of his stomach emptied of food.  
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Then think of ENARAX. For ENARAX was formulated to help you control precisely this clinical picture. ENARAX provides oxyphenyclimimine, the inherently long-acting anticholinergic (up to 9 hours of actual achlorhydria<sup>1</sup>) . . . plus Atarax, the tranquilizer that doesn't stimulate gastric secretion.

Thus, with b.i.d. dosage, you provide continuous antisecretory/antispasmodic action and safely alleviate anxiety . . . with these results: ENARAX has been proved effective in 92% of G.I. patients.<sup>2-4</sup>

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(10 MG. OXYPHENCYCLIMIMINE PLUS 25 MG. ATARAX<sup>®</sup>) A SENTRY FOR THE G.I. TRACT

**dosage:** Begin with one-half tablet b.i.d.—preferably in the morning and before retiring. Increase dosage to one tablet b.i.d. if necessary, and adjust maintenance dose according to therapeutic response. Use with caution in patients with prostatic hypertrophy and only with ophthalmological supervision in glaucoma.

**supplied:** In bottles of 60 black-and-white scored tablets. Prescription only.

**References:** 1. Steigmann, F., et al.: *Am. J. Gastroenterol.* 33:109 (Jan.) 1960. 2. Hock, C. W.: to be published. 3. Leming, B. H., Jr.: *Clin. Med.* 6:423 (Mar.) 1959. 4. Data in Roerig Medical Department Files.

<sup>†</sup>brand of hydroxyzine

FOR HEMATOPOIETIC STIMULATION  
WHERE OCCULT BLEEDING IS PRESENT

**HEPTUNA<sup>®</sup> PLUS**

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**in premenstrual  
tension  
clinicians report  
rapid relief with**



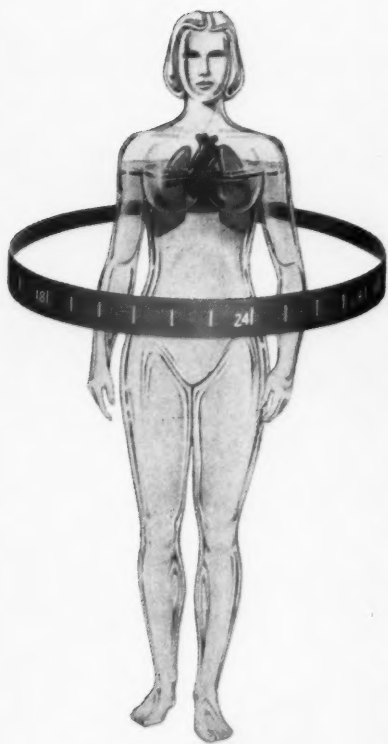
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*Fuchs, M. and Moyer, J.:  
Diseases of the Chest 35:314, (March) 1959.*

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brand of prochlorperazine

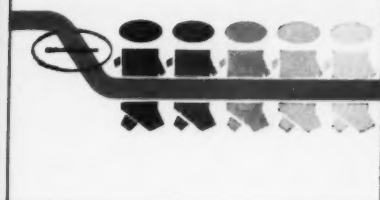
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**ADMINISTRATION AND DOSAGE:** Familiarity with criteria for patient selection, continued close medical supervision, and observance by the patient of good dietary and hygienic habits are essential.

Average maintenance dosage is 100-500 mg. daily. For most patients the recommended starting dose is 250 mg. given once daily. Geriatric patients should be started on 100-125 mg. daily. A priming dose is not necessary and should not be used; most patients should be maintained on 500 mg. or less daily. Maintenance dosage above 750 mg. should be avoided. Before initiating therapy, consult complete dosage information.

**SIDE EFFECTS:** In the main, side effects, e.g., hypoglycemia, gastrointestinal intolerance, and neurologic reactions, are related to dosage. They are not encountered frequently on presently recommended low dosage. There have been, however, occasional cases of jaundice and skin eruptions primarily due to drug sensitivity; other side effects which may be idiosyncratic are occasional diarrhea (sometimes sanguineous) and hematologic reactions. Since sensitivity reactions usually occur within the first six weeks of therapy, a time when the patient is under very close supervision, they may be readily detected. Should sensitivity reactions be detected, **DIABINESE** should be discontinued.

**PRECAUTIONS AND CONTRAINDICATIONS:** If hypoglycemia is encountered, the patient must be observed and treated continuously as necessary, usually 3-5 days, since **DIABINESE** is not significantly metabolized and is excreted slowly. **DIABINESE** as the sole agent is not indicated in juvenile diabetes mellitus and unstable or severely "brittle" diabetes mellitus of the adult type. Contraindicated in patients with hepatic dysfunction and in diabetes complicated by ketosis, acidosis, diabetic coma, fever, severe trauma, gangrene, Raynaud's disease, or severe impairment of renal or thyroid function. **DIABINESE** may prolong the activity of barbiturates. An effect like that of disulfiram has been noted when patients on **DIABINESE** drink alcoholic beverages.

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in all degrees  
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by itself in most  
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25 mg. HydroDIURIL, 0.125 mg. reserpine.  
One tablet one to four times a day.

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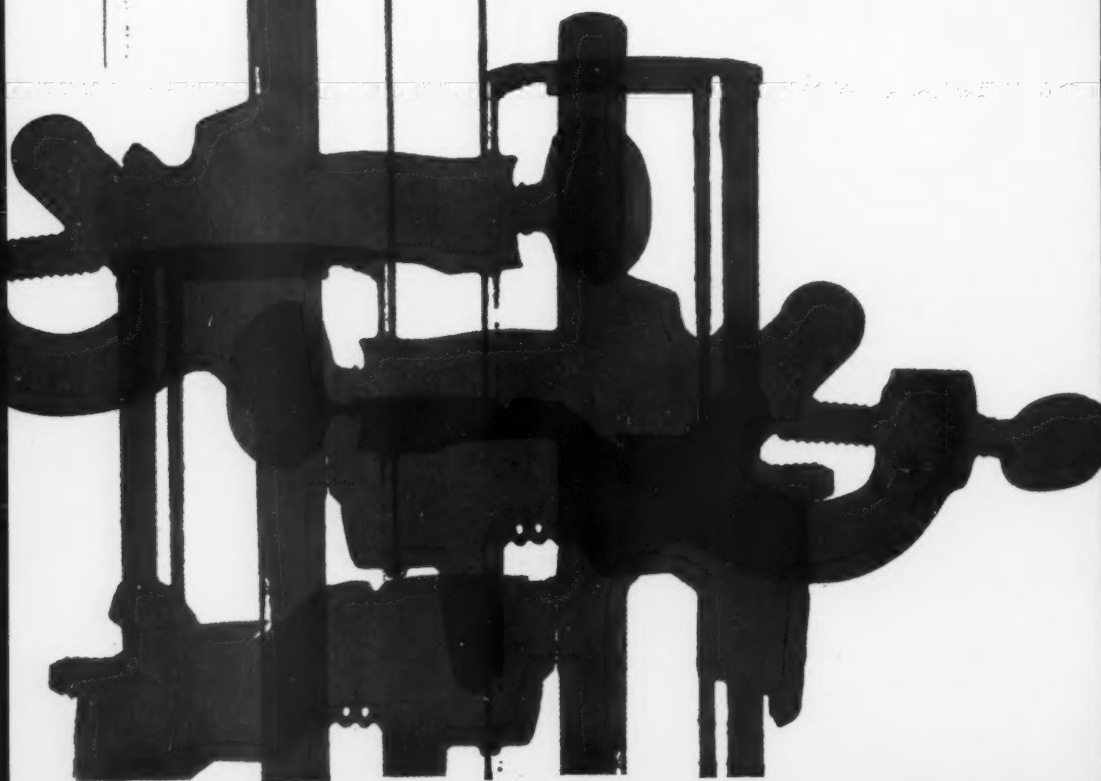


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**Published reports on Librium:** 1. T. H. Harris, *Dis. Nerv. System*, 21:(Suppl.), 3, 1960. 2. L. O. Randall, *ibid.*, p. 7. 3. J. M. Tobin, I. F. Bird and D. E. Boyle, *ibid.*, p. 11. 4. H. A. Bowes, *ibid.*, p. 20. 5. J. Kinross-Wright, I. M. Cohen and J. A. Knight, *ibid.*, p. 23. 6. H. H. Farb, *ibid.*, p. 27. 7. C. Breitner, *ibid.*, p. 31. 8. I. M. Cohen, Discussant, *ibid.*, p. 35. 9. G. A. Constant, *ibid.*, p. 37. 10. L. J. Thomas, *ibid.*, p. 40. 11. R. C. V. Robinson, *ibid.*, p. 43. 12. S. C. Kaim and I. N. Rosenstein, *ibid.*, p. 46. 13. H. E. Ticktin and J. D. Schultz, *ibid.*, p. 49. 14. J. N. Sussex, *ibid.*, p. 53. 15. I. N. Rosenstein, *ibid.*, p. 57. 16. D. C. English, *Curr. Therap. Res.*, 2:88, 1960. 17. T. H. Harris, *J.A.M.A.*, 172:1162, 1960. 18. G. L. Usdin, *J. Louisiana M. Soc.*, 112:142, 1960. 19. I. N. Rosenstein and C. W. Silverblatt, paper read at Pan American Medical Association, 35th Anniversary Congress, Mexico City, Mexico, May 2-11, 1960. 20. K. Rickels, *ibid.* 21. N. Toll, *Dis. Nerv. System*, 21:264, 1960.

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relieves uterine spasm and hypermotility by *direct* relaxant action on uterine muscle\*  
proved effective clinically with a low incidence of side effects\*

**dosage:** For menstrual cramps, give 10 or 20 mg. (1 or 2 tablets) three or four times daily 24 to 72 hours prior to expected onset of menstruation. Continue until pain has been averted.

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\*Voulgaris, D. M.: *Obst. & Gynec.* 75:220-222 (Feb.) 1960.

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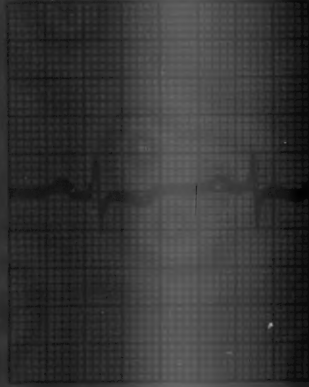
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#### References:

1. Alfaro, R. D.; Graciano, V. and Schuster, E.; Michigan Acad. Gen. Pract., Detroit, November, 1959. 2. Hersh, G.; Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 3. Horwitz, S.; Personal communication, 1959. 4. Spielman, A. D.; Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 5. Brown, E.; Michigan Acad. Gen. Pract. Symposium, Detroit, 1959. 6. Doolin, Jr., J.; Exptl. Med. & Surg. in press. 7. Swanson, J. S.; Personal communication, 1959. 8. Kroms and Storch; Personal communication, 1959.

# TENUATE

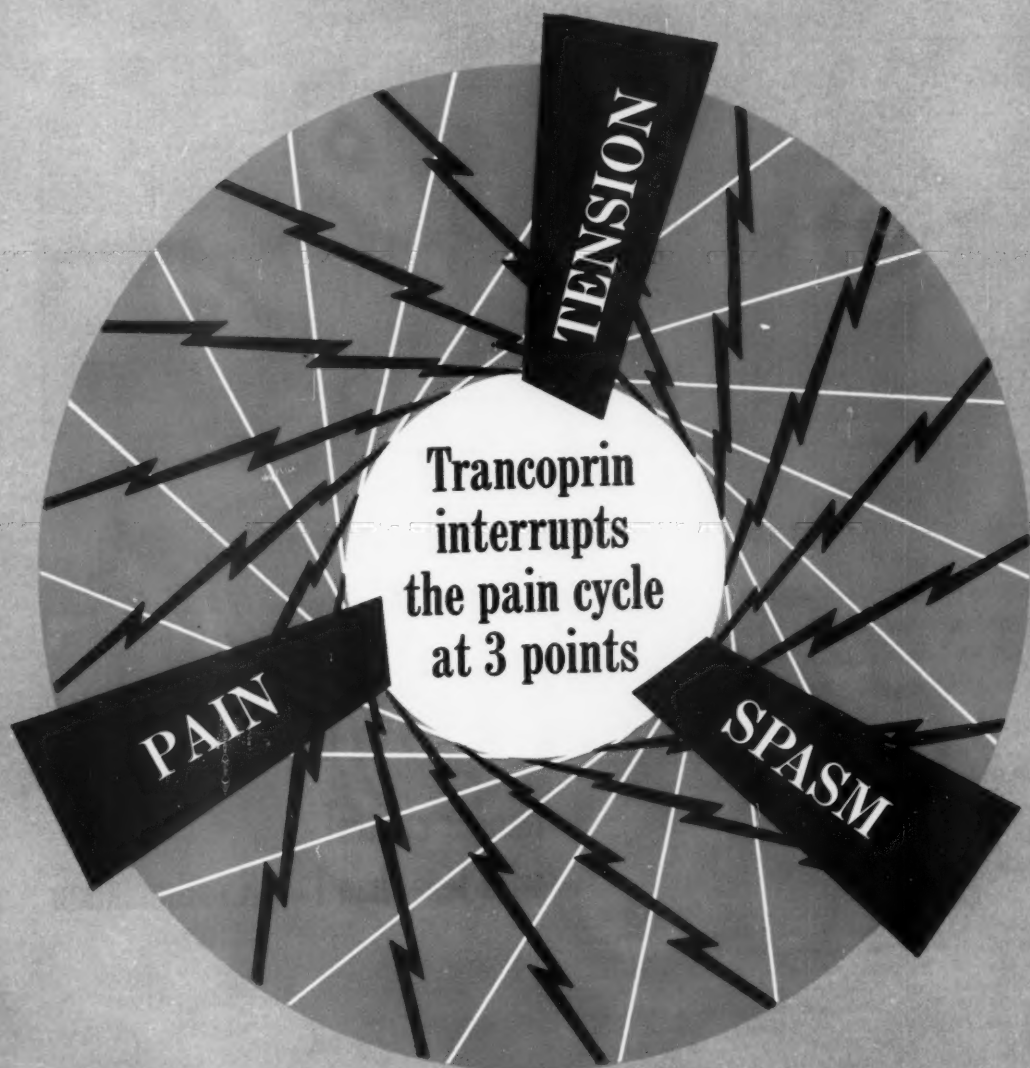
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Trancoprin is recommended for more comprehensive control of the pain complex (pain → tension → spasm) in those disorders in which tension and spasm are complicating factors, such as: headaches, including tension headaches / premenstrual tension and dysmenorrhea / low back pain, sciatica, lumbago / musculoskeletal pain associated with strains or sprains, myositis, fibrositis, bursitis, trauma, disc syndrome and myalgia / arthritis (rheumatoid or hypertrophic) / torticollis / neuralgia.

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The usual adult dosage is 2 Trancoprin tablets three or four times daily. The dosage for children from 5 to 12 years of age is 1 tablet three or four times daily. Trancoprin is so well tolerated that it may be taken on an empty stomach for quickest effect. The relief of symptoms is apparent in from fifteen to thirty minutes after administration and may last up to six hours or longer.

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## Trancoprin Tablets / non-narcotic analgesic

**References:** 1. DeNyse, D. L.: *M. Times* 87:1512, Nov., 1959. 2. Ganz, S. E.: *J. Indiana M. A.* 52:1134, July, 1959. 3. Gruenberg, Friedrich: *Current Therap. Res.* 2:1, Jan., 1960. 4. Kearney, R. D.: *Current Therap. Res.* 2:127, April, 1960. 5. Lichtman, A. L.: *Kentucky Acad. Gen. Pract. J.* 4:28, Oct., 1958. 6. Mullin, W. G., and Epifano, Leonard: *Am. Pract. & Digest Treat.* 10:1743, Oct., 1959. 7. Shanaphy, J. F.: *Current Therap. Res.* 1:59, Oct., 1959. 8. Collective Study, Department of Medical Research, Winthrop Laboratories. 9. Hergesheimer, L. H.: An evaluation of a muscle relaxant (Trancopal) alone and with aspirin (Trancoprin) in an industrial medical practice, to be submitted.

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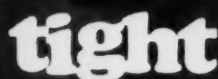
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streptomycin	resistant	
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Mandelamine	<b>sensitive</b>	
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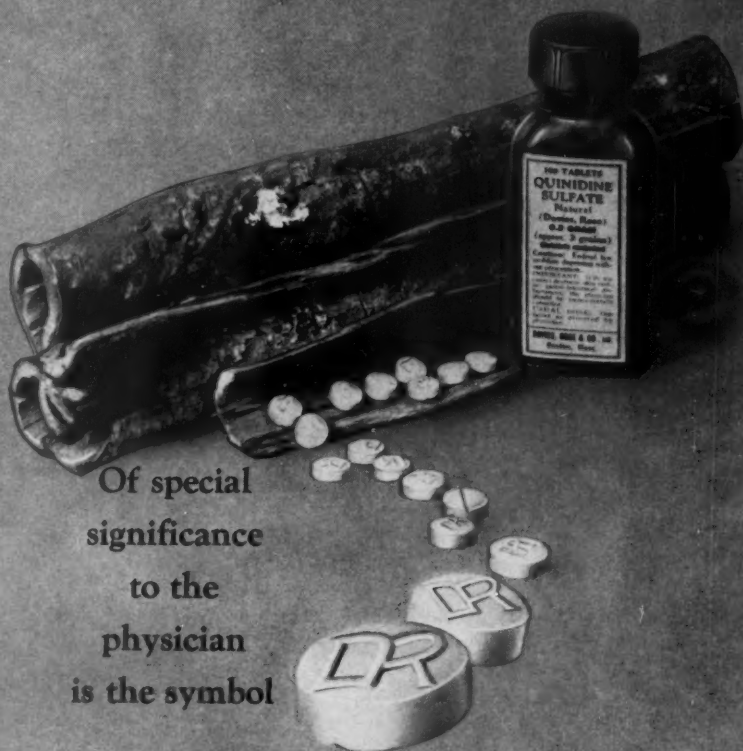
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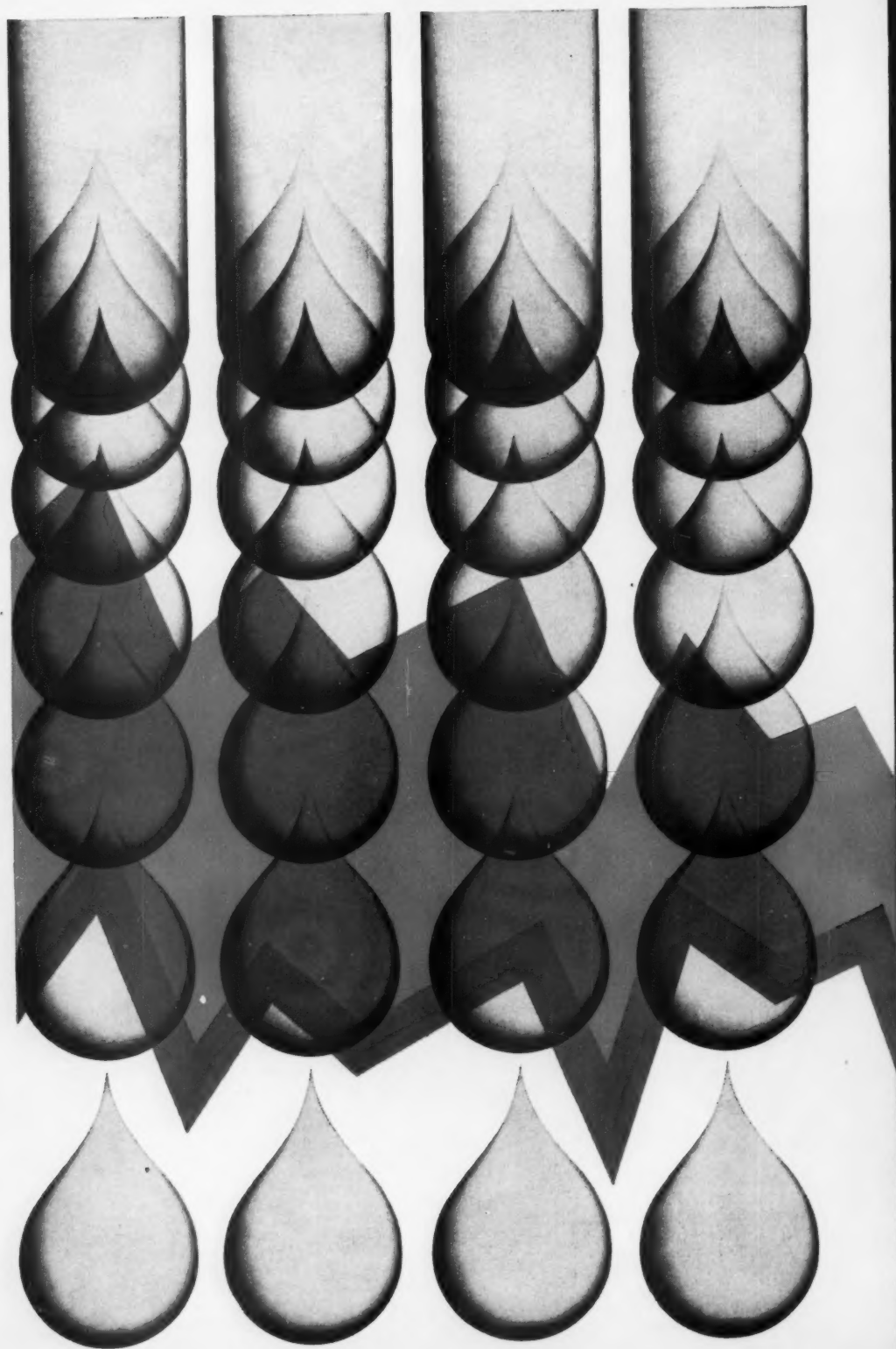
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Average adult dose: One teaspoonful after meals and at bedtime. May be habit-forming. Federal law permits oral prescription.

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**New  
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brand of chlorthalidone

**longest  
in action...  
smoothest  
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**in  
hypertension  
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**Geigy**

potent antihypertensive-saluretic

greater loss of sodium  
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A new antihypertensive-saluretic, Hygroton now enables still more effective and safer control of hypertension and edema.

**more evenly sustained therapeutic response**  
Because it has the most prolonged action of all diuretics<sup>1</sup> Hygroton exercises smoother, more evenly sustained therapeutic effect...with almost complete freedom from significant side reactions.<sup>2-4</sup>

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Hygroton produces only minimal potassium loss<sup>1,5</sup>...affords a better sodium-potassium ratio than other saluretics.<sup>5</sup>

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**affording still greater assurance of response**

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sustained control without side reactions.

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Hygroton®, brand of chlorthalidone: White, single-scored tablets of 100 mg. in bottles of 100.



Geigy, Ardsley, New York

HY 236-60



if you're  
treating  
a coccal  
infection...

you can't prescribe a more  
effective antibiotic than

# ERYTHROCIN

Erythromycin. Abbott

How much "spectrum" do you need in treating an infection? Clearly you want an antibiotic that will show the greatest activity against the offending organisms *and the least activity against non-pathogenic gastro-intestinal flora.*

Weigh these criteria — and make this comparison — when treating your next coccal infection. Erythrocin is a medium-spectrum

antibiotic, notably effective against gram-positive organisms. In this it comes close to being a "specific" for coccal infections — *which means it is delivering a high degree of activity against the majority of common infection-producing bacteria.*

And against many of the troublesome "staph" strains — a group which shows increasing resistance to penicillin and certain other antibiotics — Erythrocin continues to provide bactericidal activity. Yet, as potent as Erythrocin is, *it rarely has a disturbing effect on normal gastro-intestinal flora.* Comes in easy-to-swallow Filmtabs®, 100 and 250 mg. Usual adult dose is 250 mg. every six hours. Children, in proportion to age and weight. Won't you try Erythrocin?

®Filmtab—Film-sealed tablets, Abbott.



To Calm the Nervous, Worrisome Elderly Patient  
...without the hazard of cumulative toxicity...

# BUTISOL<sup>®</sup> sodium<sup>®</sup>

**BUTISOL**—noncumulative—"is destroyed rapidly in the body . . . not contraindicated in the presence of renal disease . . . essentially nontoxic for the liver"<sup>1</sup>—is well suited to geriatrics.

**BUTISOL** does not produce the "confusion and disorientation"<sup>2</sup> frequently associated with the use of phenobarbital in the aged.

**BUTISOL** "provided the highest rating (therapeutic index) of sedatives studied for control of anxiety and insomnia by daytime dosage" in a 5-year study<sup>3</sup>, because it showed the lowest incidence of side effects and least likelihood of cumulative toxicity.

**BUTISOL Sodium<sup>®</sup> Tablets • Repeat-Action Tablets • Elixir • Capsules**

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**McNEIL LABORATORIES, INC. Philadelphia 32, Pa.**



**McNEIL**

# In over five years

## Proven

in more than  
750 published clinical studies

## Effective

FOR RELIEF OF ANXIETY  
AND TENSION

## Outstandingly Safe

**For your reference: controlled studies on Miltown.**

1. Blumberg, N. et al.: *Fed. Proc.* 17:351, March 1958. 2. Boyd, L. J. et al.: *Am. J. Cardiol.* 3:229, Feb. 1959. 3. Brick, H. et al.: *J. Social Therapy* 4:190, 1958. 4. Bulla, J. D. et al.: *Am. Pract. & Digest Treat.* 10:1961, Nov. 1959. 5. Ewing, J. A. and Haizlip, T. M.: *Am. J. Psychiat.* 114:835, March 1958.

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# of clinical use...

- 1 simple dosage schedule produces rapid, reliable tranquilization without unpredictable excitation
- 2 no cumulative effects, thus no need for difficult dosage readjustments
- 3 does not produce ataxia, change in appetite or libido
- 4 does not produce depression, Parkinson-like symptoms, jaundice or agranulocytosis
- 5 does not impair mental efficiency or normal behavior

.....[double-blind]

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*Usual dosage:* One or two 400 mg. tablets t.i.d.  
*Supplied:* 400 mg. scored tablets, 200 mg. sugar-coated tablets. Also as MEPROTABS®—400 mg. unmarked, coated tablets; and as MEPROSPAN®—400 mg. and 200 mg. continuous release capsules.

®TRADE-MARK

## Miltown®

meprobamate [Wallace]



WALLACE LABORATORIES / Cranbury, N. J.

## Blood pressure that goes up with stress often comes down with SERPASIL®

(reserpine CIBA)

One reason that many cases of hypertension respond to Serpasil is that many cases are associated with stress. Stress situations produce stimuli which pass through the sympathetic nerves, constricting blood vessels, and increasing heart rate. Hyperactivity of the sympathetic nervous system may elevate blood pressure; if prolonged, this may produce frank hypertension. By blocking the flow of excessive stimuli to the sympathetic nervous system, Serpasil guards against stress-induced vasoconstriction, brings blood pressure down slowly and gently.

In mild to moderate hypertension, Serpasil is basic therapy, effective alone "...in about 70 per cent of cases..."\*

In severe hypertension, Serpasil is valuable as a primer. By adjusting the patient to the physiologic setting of lower pressure, it smooths the way for more potent antihypertensives.

In all grades of hypertension, Serpasil may be used as a background agent. By permitting lower dosage of more potent antihypertensives, Serpasil minimizes the incidence and severity of their side effects.

\*Coan, J. P., McAlpine, J. C., and Boone, J. A.: J. South Carolina M. A. 51:417 (Dec.) 1955.

/S2000

Complete information available on request.


CIBA  
SUMMIT, N. J.



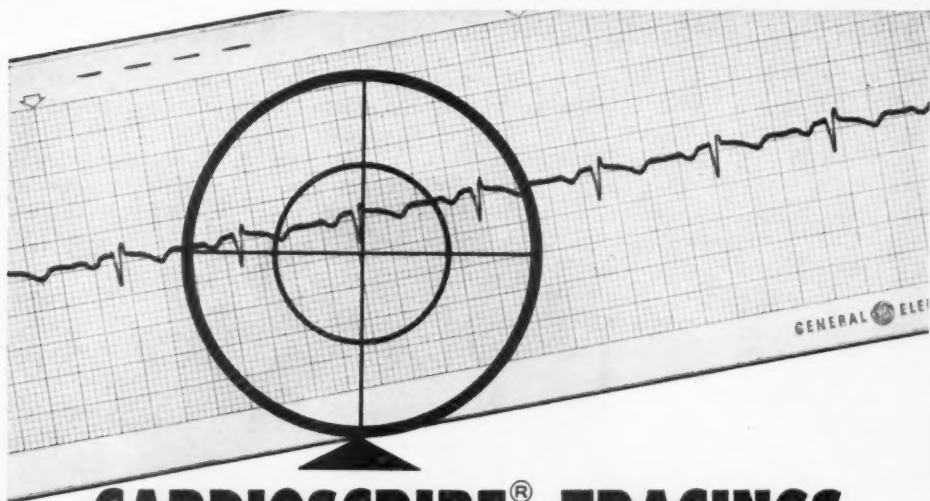


## when bacterial diarrheas leave little patients limp **Furoxone® Liquid**

brand of furazolidone

• Rapid, decisive bactericidal action against an exceptionally broad range of enteric pathogens, including some now resistant to other antimicrobials • Safe for all age groups—virtually nontoxic, side effects negligible, no interference with the normal balance of intestinal flora • Liquid suspension, containing kaolin and pectin, may be mixed with infant formula; passes through a standard nursing nipple • Dosage for both children and adults may be found in your P.D.R. 

EATON LABORATORIES, Division of The Norwich Pharmacal Company, NORWICH, N. Y.



## CARDIOSCRIBE® TRACINGS

...vital in the war  
against heart disease

To facilitate early diagnosis of heart disease, cardiograms are becoming an integral part of every *complete* physical examination. This is particularly true when the patient is over 40—a time when many enemies of the heart resort to open warfare.

The G-E Cardioscribe has been specially designed to provide you with tracings that are completely reliable . . . simpler and faster to take. One-millivolt standardization is accurately verified by built-in, direct-reading meter. A separate chest lead-transfer switch contributes greatly to operator efficiency, and is especially useful for handling large numbers of patients in a minimum of time. You can take up to 30 leads without changing electrodes — you merely turn selector switches!

And Cardioscribe's 50-mm paper gives you *full-scale* recordings.

*Swing-out* paper drive in the back facilitates loading. You can't damage the delicate stylus since the hinged drive swings out and away from it. Nothing to disassemble.



For further information on the *always-reliable* Cardioscribe, see your G-E x-ray representative. Or, write X-Ray Department, General Electric Company, Milwaukee 1, Wis., for Pub. M-115.

*Progress Is Our Most Important Product*

GENERAL  ELECTRIC



...for more effective pain relief

# Ascriptin<sup>®</sup> (RORER)

particularly suited for arthritic patients

Combining the antacid MAALOX<sup>®</sup> with aspirin increases both absorption and utilization of the salicylate. As a result, ASCRIPTIN acts twice as fast as plain aspirin and analgesic action lasts much longer due to maintenance of higher plasma salicylate levels.

Gastric irritation seldom occurs with ASCRIPTIN

even if large doses are given for long periods.

Of particular value in arthritis and rheumatic disease, ASCRIPTIN is an excellent salicylate for routine use.

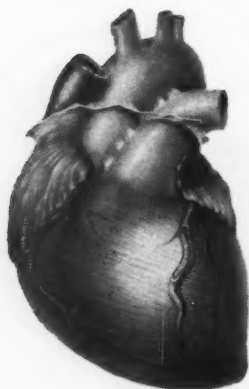
Formula: Acetylsalicylic acid 0.30 Gm., MAALOX (magnesium-aluminum hydroxides) 0.15 Gm. Offered: Bottles of 100 and 500.



**WILLIAM H. RORER, INC.**

Philadelphia 44, Pa.

Please Mention this Journal when writing to Advertisers



#### IN ANGINA PECTORIS AND CORONARY INSUFFICIENCY

... the treatment must go further than vasodilation alone. It should also control the patient's ever-present anxiety about his condition, since anxiety itself may bring on further attacks.



#### AFTER MYOCARDIAL INFARCTION

... it is frequently not enough to boost blood flow through arterial offshoots and establish new circulation. The disabling fear and anxiety that invariably accompany the condition must be reduced, or the patient may become a chronic invalid.

## Protects your coronary patient better than vasodilation alone

**Unless the coronary patient's ever-present anxiety about his condition can be controlled, it can easily induce an anginal attack or, in cases of myocardial infarction, considerably delay recovery.**

This is why Miltrate gives better protection for the heart than vasodilation alone in coronary insufficiency, angina pectoris and postmyocardial infarction. Miltrate contains not only PETN (pentaerythritol tetranitrate), acknowledged as basic therapy for long-acting vasodilation. What is more important — Miltrate provides Miltown, a tranquilizer of *proven* effectiveness in relieving anxieties, fear and day-to-day tension in over 600 clinical studies.

Thus, your patient's cardiac reserve is protected against his fear and concern about his condition...and his operative arteries are dilated to enhance myocardial blood supply.

**Supplied:** Bottles of 50 tablets. Each tablet contains 200 mg. Miltown and 10 mg. pentaerythritol tetranitrate.

**Dosage:** 1 or 2 tablets q.i.d. before meals and at bedtime, according to individual requirements.

#### REFERENCES

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# Miltrate®

Miltown® (meprobamate) + PETN



WALLACE LABORATORIES / Cranbury, N. J.



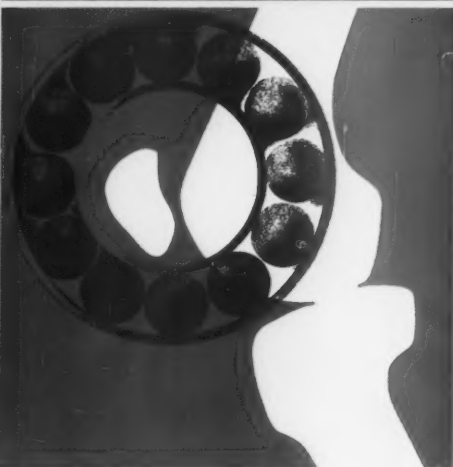
in arthritis and allied disorders

**Butazolidin®**  
**Geigy**

Proved by a Decade of Experience  
Confirmed by 1700 Published Reports  
Attested by World-Wide Usage

Since its anti-inflammatory properties were first noted in Geigy laboratories 10 years ago, time and experience have steadily fortified the position of Butazolidin as a leading nonhormonal anti-arthritic agent. Indicated in both chronic and acute forms of arthritis, Butazolidin is noted for its striking effectiveness in relieving pain, increasing mobility and halting inflammatory changes.

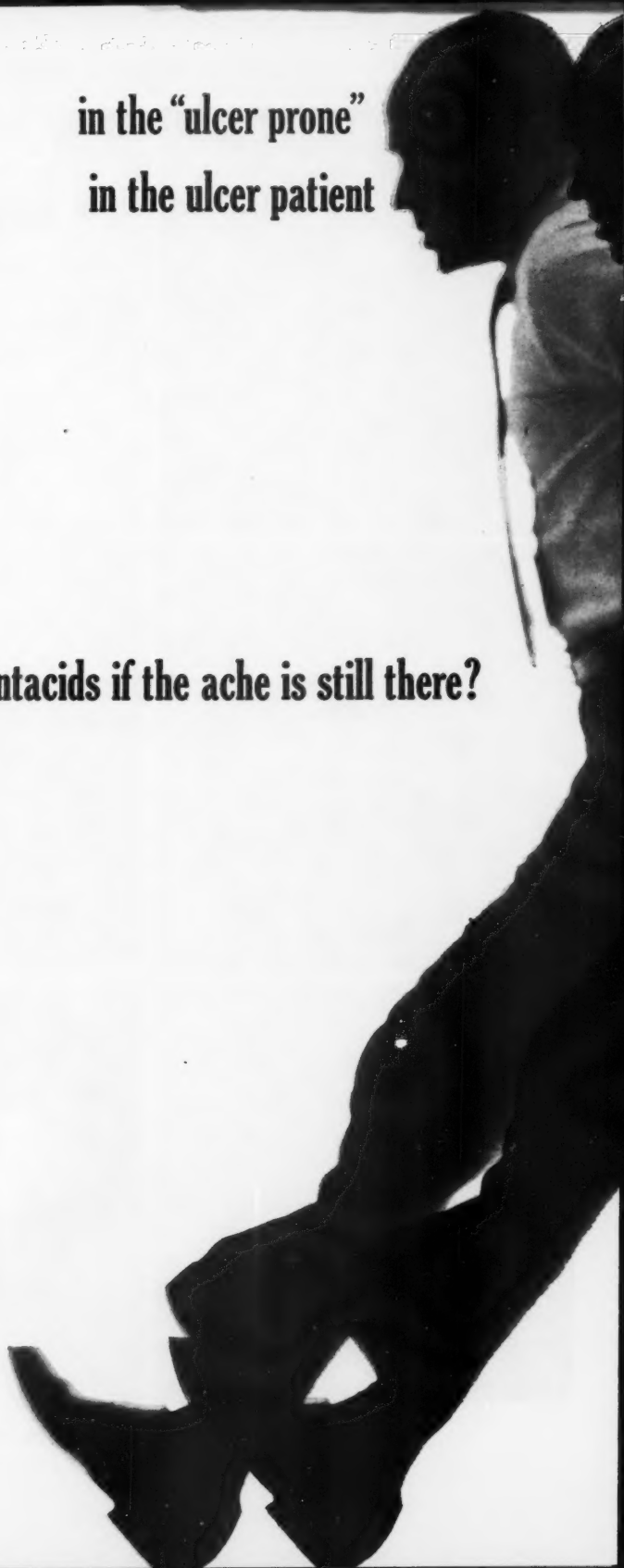
Butazolidin®, brand of phenylbutazone:  
Red, sugar-coated tablets of 100 mg;  
Butazolidin® Altra; Orange and white  
capsules containing Butazolidin 100 mg;  
dried aluminum hydroxide gel 100 mg;  
magnesium trisilicate 150 mg;  
homatropine methylbromide 1.25 mg.



Please Mention this Journal when writing to Advertisers

**in the "ulcer prone"  
in the ulcer patient**

**...what good are antacids if the ache is still there?**





# Kolantyl

**much more than an antacid  
blocks all three sources of  
pre-ulcer and ulcer pain**

Antacid relief is only partial, because acid causes only part of your patient's discomfort. In almost every case, he suffers with painful G. I. spasm, too.

Kolantyl stops it. Of course, most antacids will soothe irritated mucosa.

Kolantyl, however, does more... helps prevent further erosion, promotes healing. And when you prescribe Kolantyl, your patients will take it gladly. You see, Kolantyl tastes extra good.

**Dosage:** 1 tablespoonful or 2 tablets, every three hours, as needed.

**Formula:** Each tablet or 10 cc. Gel

(2 teaspoonfuls) contains:

Bentyl (dicyclomine) Hydrochloride 5 mg.

Aluminum Hydroxide Gel, Dried.....400 mg.

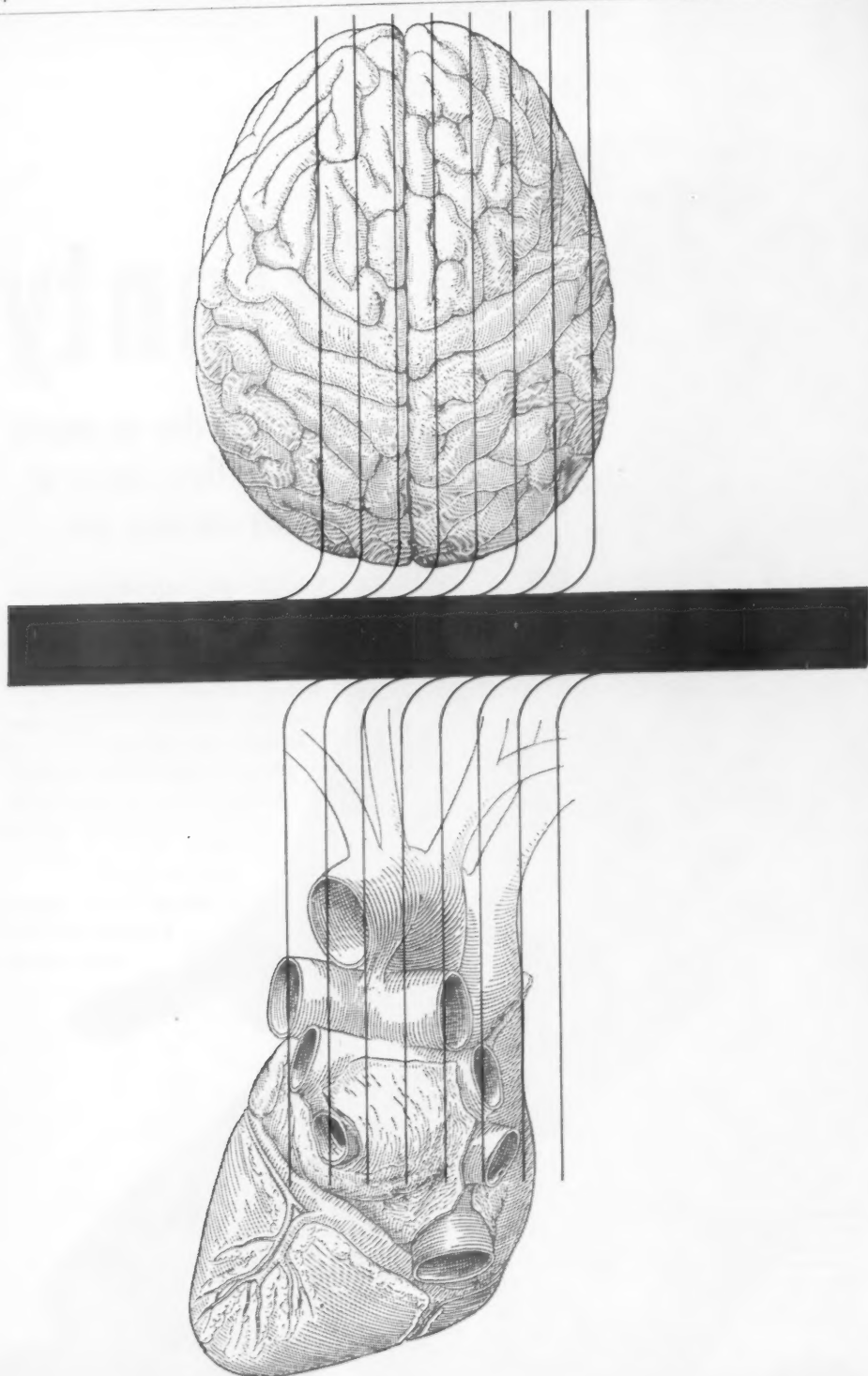
Magnesium Oxide, Heavy.....200 mg.

Sodium Lauryl Sulfate..... 25 mg.

Methylcellulose .....100 mg.

TRADEMARKS: BENTYL®, KOLANTYL®

**Merrell** THE WM. S. MERRELL COMPANY • Cincinnati, Ohio/St. Thomas, Ontario



## To lift depression

*Marplan covers the broad range of depressive states, including seemingly mild but progressively deteriorating conditions, many "masked" depressions, suicidal ideation, as well as depressions necessitating hospitalization. It increases accessibility of the withdrawn or regressed individual, improving rapport between physician and patient.*

*Where prior therapy has failed, Marplan often produces dramatic results. Prompt social recovery, e.g., was achieved with Marplan in a "severe, chronic, obsessive-compulsive neurotic illness" of 20 years' duration, disabling the patient for 12 years; previous treatment had included tranquilizers and ECT.<sup>6</sup>*

A single agent, with two distinct primary effects, for two important clinical indications

# Marplan

a happy balance of potency/safety

## To control pain in "difficult" cases of angina pectoris

*Marplan prevents anginal pain,<sup>1-3</sup> increases exercise tolerance<sup>2,4,5</sup> and reduces nitroglycerin requirements.<sup>2,3</sup> It is designed for use on a continuous schedule by patients with moderately severe to intractable angina pectoris.*

*Marplan improves the mental climate:* Not only could anginal patients placed on Marplan "... do more than formerly..."<sup>4</sup> but they also felt better, were more alert, more cheerful.<sup>2,4</sup> The loss of pain as a warning signal against undue exertion may be balanced by close patient supervision, strict guidance, and by maintaining all restrictions of activity in force prior to Marplan therapy.

Marplan has been shown to be considerably more potent than certain other amine oxidase regulators. One might expect such potency to be associated clinically with increased side effects. Actually, Marplan strikes a happy balance of potency and safety, exhibiting a marked decrease in certain of the hydrazine side reactions; there have been no reports of hepatitis attributable to Marplan. Nevertheless, all precautions set forth in the product literature should be strictly observed.

Consult literature and dosage instructions, available on request, before prescribing.

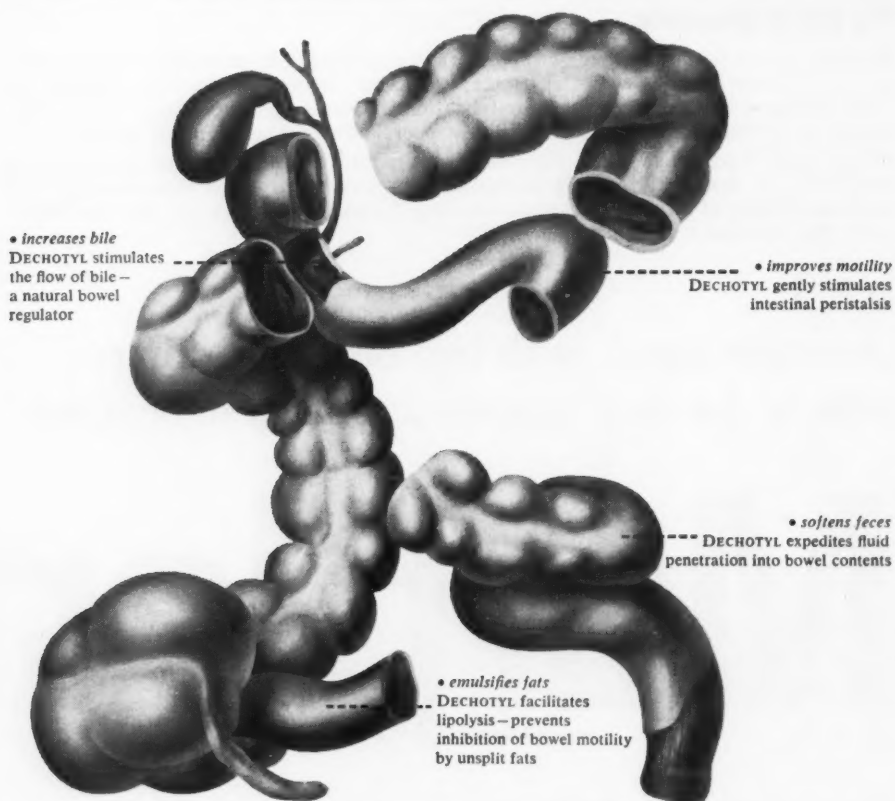
*Selected bibliography from 38 published papers: 1. W. Hollander and R. W. Wilkins, in J. H. Moyer, Ed., Hypertension, Philadelphia, W. B. Saunders Co., 1959, p. 399. 2. R. W. Oblath, paper read at American Therapeutic Society, 60th Annual Meeting, Atlantic City, N. J., June 6, 1959. 3. N. Bloom, Virginia M. Month., 87:23, 1960. 4. G. C. Griffith, Clin. Med., 6:1555, 1959. 5. G. C. Griffith, Dis. Nerv. System, 21:(Suppl.), 101, 1960. 6. L. Alexander and S. R. Lipsett, Dis. Nerv. System, 20:(Suppl.), 26, 1959.*

MARPLAN®—1-benzyl-2-(5-methyl-3-isoxazolylicarbonyl) hydrazine



ROCHE  
LABORATORIES

Division of Hoffmann-La Roche Inc.



helps free your patient from both...  
constipation and laxatives

# DECHOTYL<sup>®</sup>

TRABLETS<sup>®</sup>

well tolerated...gentle transition to normal bowel function



Recommended to help convert the patient—naturally and gradually—to healthy bowel habits. Regimens of one week or more are suggested to assure maintenance of normal rhythm and to avoid the repetition of either laxative abuse or constipation.

**Average adult dose:** Two TRABLETS at bedtime as needed or as directed by a physician. Action usually is gradual, and some patients may need 1 or 2 TRABLETS 3 or 4 times daily.

**Contraindications:** Biliary tract obstruction; acute hepatitis.

DECHOTYL TRABLETS provide 200 mg. DECHOLIN,<sup>®</sup> (dehydrocholic acid, AMES), 50 mg. desoxycholic acid, and 50 mg. dioctyl sodium sulfosuccinate, in each trapezoid-shaped, yellow TRABLET. Bottles of 100.

\*AMES T.M. for trapezoid-shaped tablet.

**AMES**  
COMPANY, INC.  
Elkhart • Indiana  
Toronto • Canada



64160



# safe and practical treatment of the postcoronary patient

A basic characteristic of the postcoronary patient, whether or not cholesterol levels are elevated, is his inability to clear fat from his blood stream as rapidly as the normal subject.<sup>1-3</sup> Figure #1 graphically illustrates this difference in fat-clearing time by comparing atherosclerotic and normal subjects after a fat meal.<sup>3</sup>

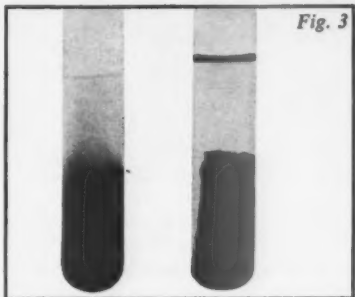
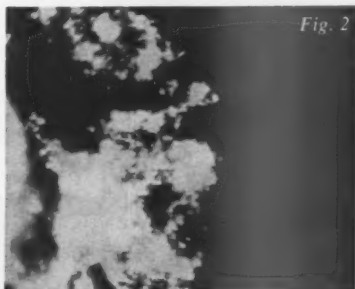
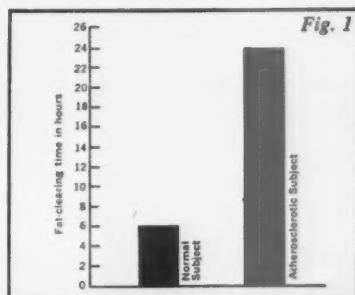
"Slow clearers" gradually accumulate an excess of fat in the blood stream over a period of years as each meal adds an additional burden to an already fat-laden serum. As shown in figure #2, the blood literally becomes saturated with large fat particles, presenting a dual hazard to the atherosclerotic patient: the long-term danger of deposition of these fats on the vessel walls,<sup>4</sup> and the more immediate risk of high blood fat levels after a particularly heavy meal possibly precipitating acute coronary embarrassment.<sup>5</sup>

In figure #3, the test tube at the left contains lipemic serum, while the one at the right contains clear, or normal serum. If serum examined after a 12-hour fasting period presents a milky appearance, this is a strong indication that the patient clears fat slowly and is a candidate for antilipemic therapy in an effort to check a potentially serious situation.

'Clarín', which is heparin in the form of a *sublingual tablet*, has been demonstrated to clear lipemic serum.<sup>2,6,7</sup> Furthermore, a two-year study using matched controls resulted in a statistically significant reduction of recurrent myocardial infarction in 130 patients treated with 'Clarín'.<sup>8</sup>

'Clarín' therapy is simple and safe, requiring no clotting-time or prothrombin determinations. Complete literature is available to physicians upon request.

**References:** 1. Anfinsen, C. B.: Symposium on Atherosclerosis, National Academy of Sciences, National Research Council Publication 338, 1955, p. 218. 2. Berkowitz, D.; Likoff, W., and Spitzer, J. J.: Clin. Res. 7:225 (Apr.) 1959. 3. Stutman, L. J., and George, M.: Clin. Res. 7:225 (Apr.) 1959. 4. Wilkinson, C. F., Jr.: Annals of Int. Med. 45:674 (Oct.) 1956. 5. Kuo, P. T., and Joyner, C. R., Jr.: J.A.M.A. 163:727 (March 2) 1957. 6. Fuller, H. L.: Angiology 9:311 (Oct.) 1958. 7. Shaftel, H. E., and Selman, D.: Angiology 10:131 (June) 1959. 8. Fuller, H. L.: Circulation 20:699 (Oct.) 1959.



**Indication:** For the management of hyperlipemia associated with atherosclerosis, especially in the postcoronary patient.

**Dosage:** After each meal, hold one tablet under the tongue until dissolved.

**Supplied:** 'Clarín' is supplied in bottles of 50 pink, sublingual tablets, each containing 1500 I.U. of heparin potassium.

\*Registered trade mark. Patent applied for.

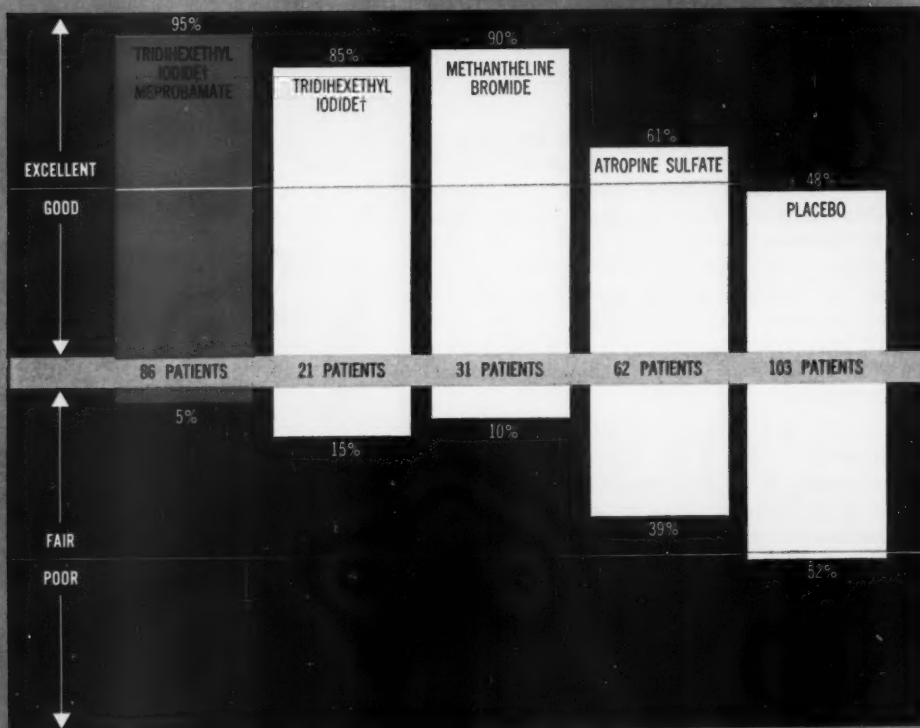
*Thos. Leeming & Co., Inc.*  
New York 17, N. Y.

# Clarín\*

(sublingual heparin potassium, Leeming)

# clinically proven efficacy...

in relieving tension... curbing hypermotility and excessive secretion in G. I. disorders



**PATHIBAMATE** combines two highly effective and well-tolerated therapeutic agents:

**Meprobamate**—widely accepted tranquilizer and

**PATHILON** tridihexethyl chloride—anticholinergic noted for its effect on motility and gastrointestinal secretion with few unwanted side effects.

**Contraindications:** glaucoma, pyloric obstruction, and obstruction of the urinary bladder neck.

Two available dosage strengths permit adjusting therapy to the G.I. disorder and degree of associated tension.

Where a minimal meprobamate effect is preferred...

**PATHIBAMATE-200** Tablets: 200 mg. of meprobamate; 25 mg. of **PATHILON**

Where a full meprobamate effect is preferred...

**PATHIBAMATE-400** Tablets: 400 mg. of meprobamate; 25 mg. of **PATHILON**

**Dosage:** Average oral adult dose is 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

# Pathibamate® 400/200

meprobamate with **PATHILON**® tridihexethyl chloride Lederle

# *..clinically proven safety*

The efficacy of **PATHIBAMATE** has been confirmed clinically in duodenal ulcer, gastric ulcer, intestinal colic, spastic and irritable colon, ileitis, esophageal spasm, anxiety neurosis with gastrointestinal symptoms, and gastric hypermotility.

Pictured are the results obtained with the **PATHILON** (tridihexethyl iodide)-meprobamate combination† in a double-blind study of 303 ulcer patients, extending over a period of 36 months.\* They clearly demonstrate the efficacy of **PATHIBAMATE** in controlling the symptoms.

SIDE EFFECTS	TRIDIHEXETHYL IODIDE† MEPROBAMATE	TRIDIHEXETHYL IODIDE†	METHANTHELIN BROMIDE	ATROPINE SULFATE	PLACEBO
DRY MOUTH	1%	5%	72%	46%	5%
STOMATITIS	1%	0%	28%	14%	0%
VISUAL DISTURBANCES	0%	0%	50%	34%	1%
URINARY RETENTION	0%	0%	18%	11%	1%
DROWSINESS	20%	0%	0%	0%	0%
COMPLICATIONS OR SURGERY					
HEMORRHAGE	0%	9%	3%	9%	10%
PERFORATION	0%	0%	0%	6%	0%
OPERATION	0%	5%	5%	14%	2%
RECURRENCES					
NONE	28%	23%	25%	17%	26%
FEWER AND Milder	67%	62%	52%	37%	24%
SAME OR MORE	5%	15%	23%	46%	50%

\*Atwater, J. S., and Carson, J. M.: Therapeutic Principles in Management of Peptic Ulcer. *Am. J. Digest. Dis.* 4:1055 (Dec.) 1959.

†**PATHILON** is now supplied as tridihexethyl chloride instead of the iodide, an advantage permitting wider use, since the latter could distort the results of certain thyroid function tests.



**LEDERLE LABORATORIES**, A Division of **AMERICAN CYANAMID COMPANY**, Pearl River, New York

## *control the tension — treat the trauma*

## this hypertensive patient prefers Singoserp

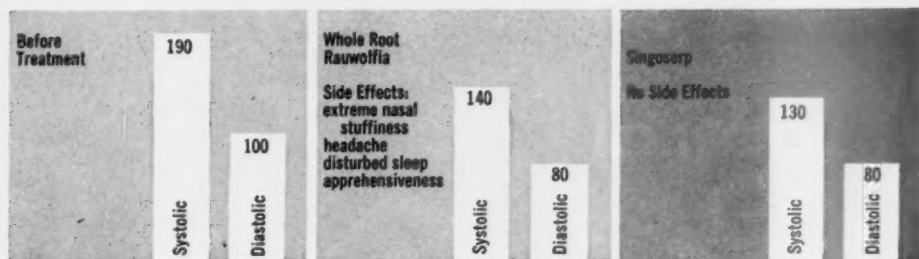
**Patient's comment:** "The other drug [whole root rauwolfia] made me feel lazy. I just didn't feel in the mood to make my calls. My nose used to get stuffed up, too. This new pill [Singoserp] doesn't give me any trouble at all."

Photo used with patient's permission.



## ...and so does his physician

**Clinician's report:** J.M., a salesman, had a 16-year history of hypertension and was rejected by the U.S. Army because of high blood pressure. When treated with whole root rauwolfia, patient had satisfactory blood pressure response but could not tolerate side effects. Singoserp, in a dose of 0.5 mg. daily, not only reduced patient's blood pressure still further, but did not produce any side effects.



---

Many hypertensive patients and their physicians prefer **Singoserp®** because it usually lowers blood pressure without rauwolfia side effects

---

SUPPLIED: Singoserp Tablets, 1 mg. (white, scored). Also available: Singoserp®-Esidrix® Tablets #2 (white), each containing 1 mg. Singoserp and 25 mg. Esidrix; Singoserp®-Esidrix® Tablets #1 (white), each containing 0.5 mg. Singoserp and 25 mg. Esidrix. **Complete information sent on request.**

Singoserp® (syrosingopine CIBA)

Singoserp®-Esidrix® (syrosingopine and hydrochlorothiazide CIBA)

2/78050X

**C I B A**  
SUMMIT, NEW JERSEY



now —  
**control**  
 virtually  
 all runaway  
 diarrheas..  
 promptly,  
 effectively  
 with



# Donnagel<sup>®</sup>



—your choice of **3** formulations

Prompt, more dependable control of virtually all diarrheas can be achieved with an appropriate DONNAGEL formula, through adsorbent, demulcent, antispasmodic and sedative effects—plus paregoric or antibiotic supplementation, as required. Early re-establishment of normal bowel function is assured—for all ages, in all seasons.

**DONNAGEL:** In each 30 cc. (1 fl. oz.):  
 Kaolin (90 gr.)..... 6.0 Gm.  
 Pectin (2 gr.)..... 142.8 mg.  
 Hyoscyamine sulfate .....0.1037 mg.  
 Atropine sulfate .....0.0194 mg.  
 Hyoscine hydrobromide ....0.0065 mg.  
 Phenobarbital (¼ gr.)..... 16.2 mg.

**DONNAGEL—PG**  
 Basic formula, plus  
 Powdered opium, U.S.P. .... 24.0 mg.  
 (Equivalent to paregoric, 6 ml.)

**DONNAGEL WITH NEOMYCIN**  
 Basic formula, plus  
 Neomycin sulfate ..... 300 mg.  
 (Equal to neomycin base, 210 mg.)

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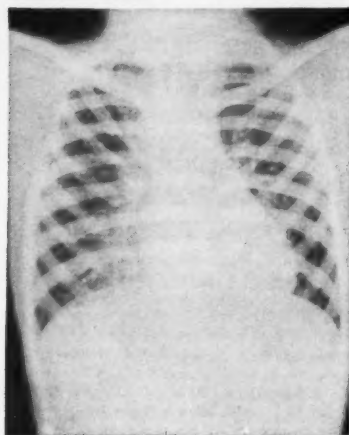
THE UPJOHN COMPANY  
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Upjohn

## Cardiac damage reduced in acute rheumatic fever



Pericarditis with pericardial effusion; roentgenogram before therapy.



Dramatic reduction in heart size after pericardial tap of only 150 cc. and 6 days of Medrol therapy.

X-rays courtesy of Lorin E. Ainger, M.D.

In 243 patients hospitalized for acute rheumatic fever, *high-dosage corticotherapy* led to regression or disappearance of significant murmurs at least twice as often as did management with salicylate, small doses of steroid, or no medication. *Early initiation of therapy* increased the percentage of patients showing cardiac improvement.<sup>1</sup>

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1. Massell, B. F.: Paper presented at A Symposium on Steroid Therapy, Chicago, Ill., May 15-16, 1959.

## INCREASED LIFE EXPECTANCY FOR HYPERTENSIVES

"Life expectancy seems to be the one criterion that is most reliable and least questioned as a method of evaluating treatment for patients with elevated blood pressure."<sup>1</sup> "It is evident that effective therapy of hypertension will prolong the life of the patient by preventing the dreaded complications of this disease in the brain, the heart and the kidneys." "There is no doubt of the prolongation of life in group 3 and 4 (Keith-Wagener-Barker) by adequate antihypertensive treatment. Some authorities report a 50 per cent, five year survival ratio for treated patients with malignant hypertension as against a 1 per cent survival ratio for untreated patients."<sup>2</sup>

Evaluation based on life expectancy is extremely difficult because of the peril of maintaining an untreated control group.<sup>1</sup> The doctor, however, can evaluate the symptoms related to the elevated blood pressure. . . . We know that retinopathy may improve, the heart may be reduced in size, the electrocardiogram may improve and in favorable cases the blood urea nitrogen level may fall.<sup>3</sup> These are reasonably objective criteria on which to base one's evaluation of treatment.<sup>1</sup>

On the succeeding page is evidence that Unitensin included in any therapeutic regimen may improve the results in hypertension as measured by a regression of objective clinical changes in a substantial proportion of the patients treated.

1. Currens, J. H.: *New England J. Med.* 261:1062, 1959.

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7. Cherny, W. B., et al.: *Obst. & Gynec.* 9:515, 1957.

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10. Finerly, F. A.: *Am. J. Med.* 17:629, 1954.

Unlike diuretics or ganglionic blocking agents, Unitensen lowers blood pressure through widespread vasorelaxation. Normal vasomotor responses are not altered, and there is no venous pooling with resulting postural hypotension.<sup>3-5</sup> Through alleviation of cerebral vasospasm, Unitensen promotes cerebral blood flow and oxygen utilization.<sup>6-9</sup> Furthermore, Unitensen increases cardiac efficiency, improves renal function and tends to arrest the progress of vascular damage.<sup>3,4,10</sup>

### Progress of Objective and Subjective Symptoms in Grades III and IV Hypertension Following Treatment with Unitensen and Unitensen-R

#### Observations in Patients\* Treated up to 2 Years

#### Observations in Patients\* Treated up to 3½ Years

##### The Course of Subjective Symptoms

Symptom	Number**	Improved	% Improved
Headache	27	21	77.7
Palpitation	20	13	65.0
Angina	15	9	60.0
Dyspnea	17	8	47.0

Number**	Improved	% Improved
43	38	88.0
29	19	65.5
21	16	76.0
27	14	51.0

##### Objective Changes Following Treatment

Finding	Number**	Improved	% Improved
Funduscular Changes	41	24	58.5
Enlarged Heart	20	13	65.0
Abnormal ECG	37	10	27.0
Proteinuria	31	12	38.7
Nitrogen Retention	17	6	35.2

Number**	Improved	% Improved
59	38	66.0
35	23	65.7
45	25	55.5
43	27	62.7
28	10	35.7

Left hand charts from Clinical Exhibit "The Ambulatory Patient with Hypertension" presented AMA Convention, San Francisco, June 22-27, 1958, by B. M. Cohen, M.D.

\*All patients in this study were initially classified as Smithwick Grades III and IV.

\*\*Expressed as the number of patients exhibiting the symptom recorded.

Right hand charts include patients previously reported who had been continuously maintained on Unitensen and Unitensen-R, plus additional patients later added to the study. From Clinical Exhibit "The Office Diagnosis and Treatment of the Patient with Hypertension" presented American Academy of General Practice, Indianapolis, March 18-19, 1959, by B. M. Cohen, M.D.

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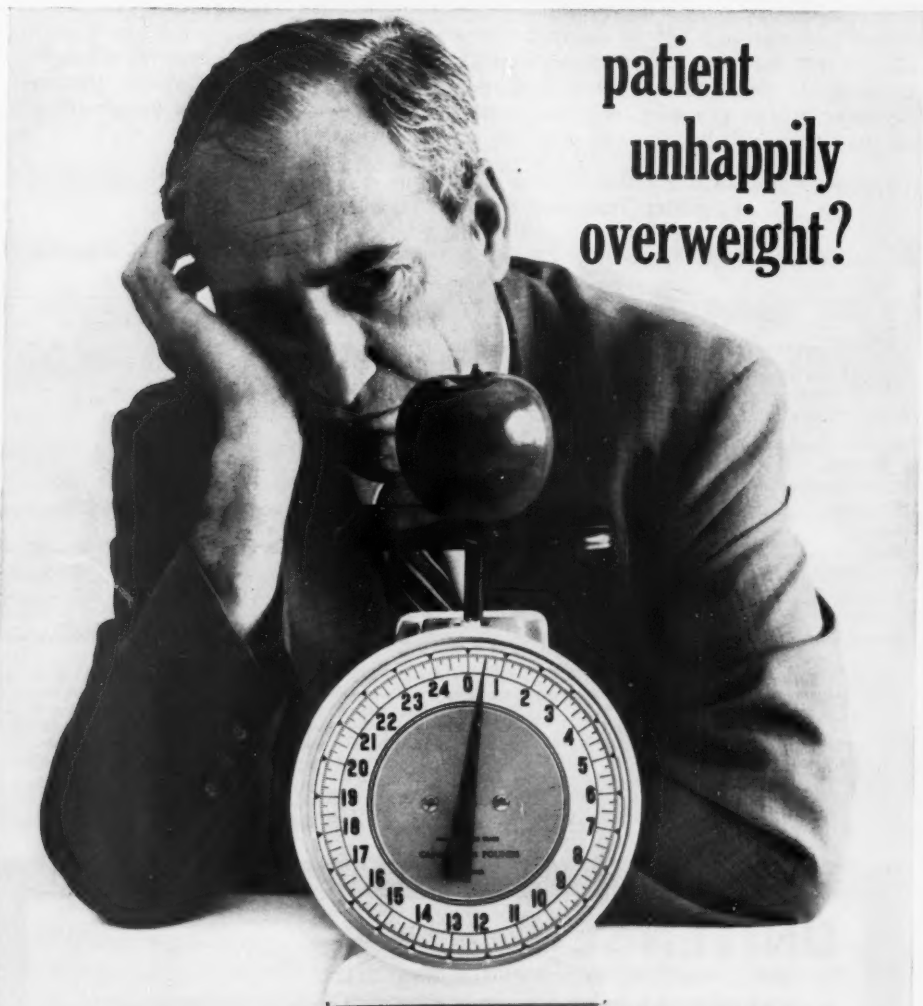
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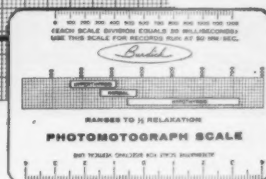
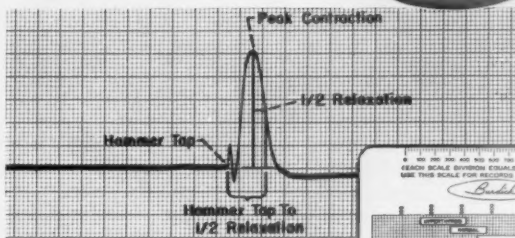
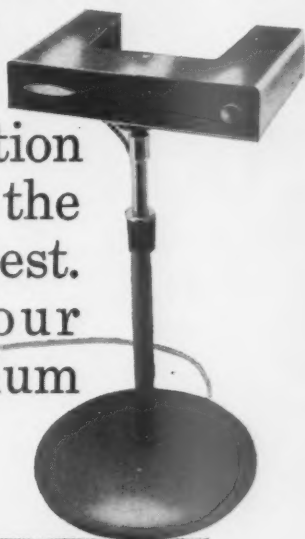
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<sup>1</sup> Douglas, H. S.: West. J. Surg. 59:238 (May) 1951.



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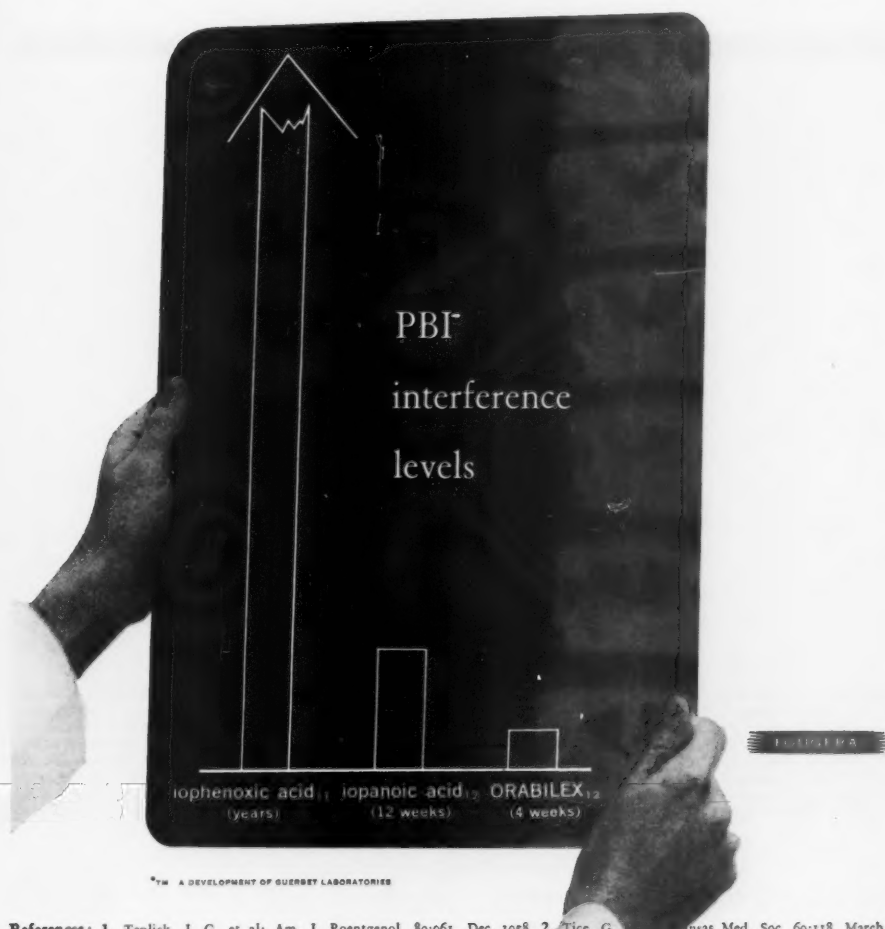
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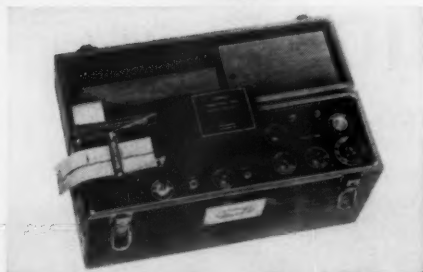
	Nov.			Dec.			Jan.			Feb.		
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<b>Course No. 5, MECHANISMS OF DISEASE:</b> Columbia University College of Physicians and Surgeons, Presbyterian Hospital, New York, N. Y.; Alfred P. Fishman, M.D., F.A.C.P., and Stanley E. Bradley, M.D., F.A.C.P., Co-Directors.										X		
<b>Course No. 6, SELECTED TOPICS IN INTERNAL MEDICINE:</b> The University of Oklahoma School of Medicine and University Hospitals, Oklahoma City, Okla.; Stewart G. Wolf, Jr., M.D., F.A.C.P., and James F. Hammarsten, M.D., F.A.C.P., Co-Directors; William O. Smith, M.D., (Associate), Associate Director.												X

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1. Bartels, E. C., and Matossian, G. S.: Gout: Six-Year Follow-Up on Probenecid (BENEMID) Therapy, Arthritis and Rheumatism 2:193, June 1959.

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2. Lockie, L. M., and Talbott, J.: Does Your Patient Have Gout?, Scientific Exhibit, American Medical Association, New York City, June 3-7, 1957.

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3. Kron, K. M., Hermann, I. F., Smith, R. T., and Richards, J. C.: Which Rheumatic Disease?, Scientific Exhibit, American Medical Association, Atlantic City, June 8-12, 1959.

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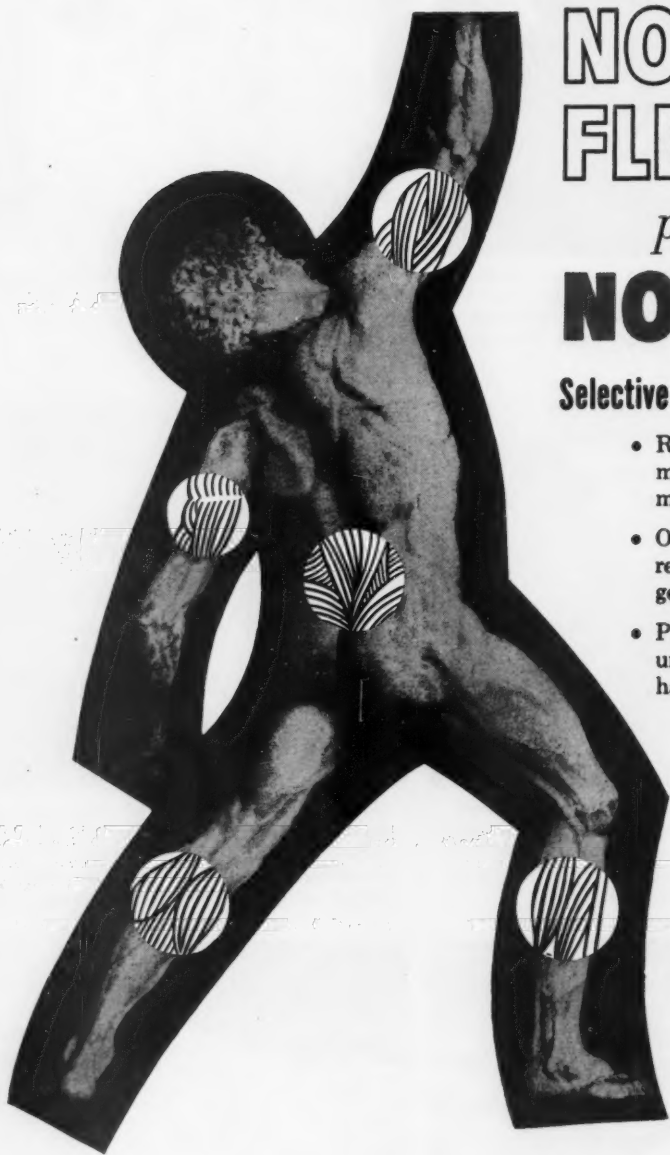
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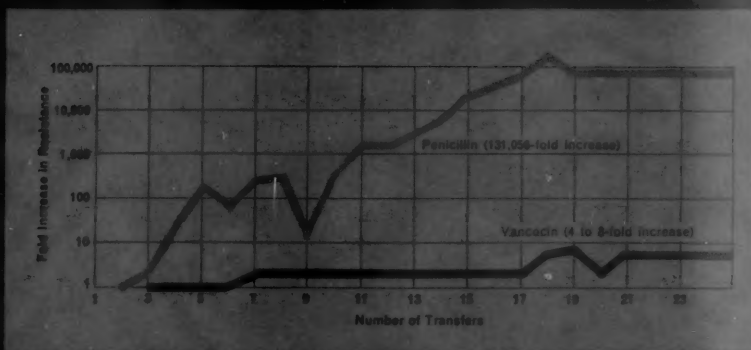
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